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THE HEART IN PROGRESSIVE MUSCULAR DYSTROPHY

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PROGRESSIVE muscular dystrophy was first described clinically by Meryon[1] in 1852. Since then, there have been many descriptions of the clinical manifestations of the disease.[2,3] Many observers[4-11] have reported a pathological process in the cardiac musculature identical to that in the skeletal musculature. More recently, there have been several clinicopathological reports with similar findings.[12-18] A survey of eleven patients with progressive muscular dystrophy studied at necropsy at this hospital by Nothacker and Netsky[19] revealed six with identical lesions in the cardiac and skeletal muscles.

Boas and Lowenberg,[20] in describing the clinical manifestations of progressive muscular dystrophy in which the heart was involved, summarized the work of Meerwein,[21] who reviewed all the 480 cases of progressive muscular dystrophy reported up to 1904. In eighty-nine of these patients some abnormality of the heart or pulse was noted. For practical purposes he divided the patients into four groups: Group I consisted of thirteen patients with abnormal pulse rates, but no cardiac murmurs or evidence of cardiac enlargement; Group II, twelve patients with definite cardiac murmurs, but no cardiac enlargement; Group III, forty-nine patients with cardiac enlargement; and Group IV of fifteen autopsied patients with definite myocardial lesions. Boas and Lowenberg[20] noted that their patients with progressive muscular dystrophy had an increase in the heart rate as measured by the cardiotachometer. Other observers have noted tachycardias and irregular pulse rhythm.[15,16,22,23] Congestive failure which responded to the administration of digitalis has also been noted in these patients.[15-18]

Early reports of electrocardiographic changes in patients with cardiac involvement in progressive muscular dystrophy were reviewed by Puddu and Mussafia.[24] They accepted only two cases reported prior to their study in 1939 as showing valid electrocardiographic abnormalities. Both of these patients had been reported by Schliephake in 1929[25]; one patient showed a diphasic T_2, and the

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second patient showed a "ventricular tachycardia with double ventricular rhythm." Puddu and Mussafia reviewed the electrocardiograms of thirty of their own patients with progressive muscular dystrophy and found only three abnormal tracings. One patient showed a Wolff-Parkinson-White syndrome with bouts of auricular tachycardia; a second patient, who had mitral stenosis, showed altered P waves with right axis deviation; and a third patient showed a prolonged P-R interval. Shank and associates[17] reported one patient with an electrocardiogram suggestive of myocardial damage, but no further description is given. A second patient exhibited a change from a left to a right axis deviation with lengthening of the Q-T interval. A patient reported in the *New England Journal of Medicine*[15] showed a "slight bundle branch block." Bevans[16] reported one patient with an electrocardiogram showing myocardial damage and two patients with electrocardiograms which showed right axis deviation with sinus tachycardia. Salvioli[26] reported changes in T_3 which, in light of more recent concepts of electrocardiography, seem to be within normal limits. Boas and Lowenberg[20] reported five of seven patients with normal electrocardiograms. One of the seven, however, showed a left axis deviation with a negative T wave in Leads II and III; a second patient showed left axis deviation with a negative T wave in Lead I. These electrocardiograms were accepted as showing evidence of myocardial damage. In these two patients the significance of the findings as an indication of dystrophic involvement of the heart is decreased because the first patient, although a young man, had hypertension (160/100 mm. Hg) and the second patient was 58 years old.

The present study is concerned with reviewing the records of patients with progressive muscular dystrophy treated at the Montefiore Hospital from 1909 to 1950 with reference to the clinical and electrocardiographic abnormalities. Two of the most interesting cases are reported in detail.

CASE REPORTS

CASE 1.—R. S., a 19-year old Negro man, was admitted to the Montefiore Hospital on March 16, 1949, with a chief complaint of difficulty in walking. At the age of 6 years, he noted that he had begun to walk on the toes because the heels "were pulled up" and the "bones in his feet turned over" and made him fall. Later, the knees became weak, and by the age of 13 years he was unable to walk. During this time contractures of the legs and thighs developed. At the age of 16 years, the patient began to lose the ability to move the shoulders; weakness subsequently progressed to the elbows and hands. The patient's past history was otherwise completely negative except for the usual childhood diseases.

Physical examination on admission revealed the following positive findings: The patient was a bedridden Negro man who appeared chronically, but not acutely, ill. The heart was not enlarged; there were no thrills or murmurs. There was a regular sinus rhythm, and the blood pressure was 110/60 mm. Hg. The lungs were clear to percussion and auscultation. Flexion deformities of the hips and knees were present, and the feet were in equinocavovarus. Marked weakness of the musculature of the lower extremities was noted. Though there were no deformities of the upper extremities, there was generalized atrophy of the musculature. Neurological examination was within normal limits; the cranial nerves were all intact, and no fibrillations were noted. Laboratory data were essentially normal. A muscle biopsy revealed evidence of progressive muscular dystrophy on histopathological study.

In the hospital little change occurred in the muscular lesions. On Aug. 23, 1949, during the course of a routine examination, it was noted that there was a systolic murmur at the apex. In

November, 1949, examination revealed the pulse rate to be 92 per minute and the blood pressure 110/70 mm. Hg. The lungs were clear. Examination of the heart revealed a forceful apical thrust; the point of maximal impulse lay just outside the left mid-clavicular line. A loud, long, moderately high-pitched systolic murmur was also heard. A regular sinus rhythm with many extrasystoles was present. The liver and spleen could not be felt. Roentgenograms of the chest revealed generalized cardiac enlargement. The Decholin circulation time was 26 seconds; the ether circulation time was 15 seconds.

One week later, the patient developed a nonproductive cough and pain in the left anterior chest which was aggravated by deep breathing. He also noted dyspnea which was relieved by assuming the upright position. Examination at this time revealed the patient to be tachypneic with a pulse rate of 124 per minute; there was splinting of the left side of the chest on respiration, and fine crackling râles were heard over the left lower anterior chest. The heart was enlarged to the left. Venous pressure in the antecubital veins was 180 mm. H_2O with a rise to 185 mm. H_2O on right upper quadrant pressure. The next day, râles were heard at both bases. A roentgenogram of the chest showed pulmonary congestion with fluid at the right base; the heart appeared slightly larger. The patient was treated with a low-salt diet, digitalis, and mercurial injections. Within the next few days he lost 4½ pounds; the tachypnea was relieved, and the lungs became clear. The numerous extrasystoles also disappeared, and the venous pressure fell to 85 mm. H_2O with no rise on right upper quadrant pressure. Since that time, he has been maintained on a low-salt diet and digitalis and has remained free of congestive heart failure.

The electrocardiogram taken Aug. 17, 1949 (Fig. 1), revealed a regular sinus rhythm with a P-R interval of 0.10 second; the QRS complex measured 0.08 second in duration. There was a deep Q in Leads I, aV_L, V_4, V_5, and V_6 and an isoelectric T in Leads I and aV_L, with a negative T in V_4, V_5, and V_6. There was a diphasic T in Leads III and aV_F. A prominent R wave was noted in Leads I and aV_R. The electrocardiogram taken July 21, 1950 (Fig. 2), revealed similar findings except that the duration of the QRS complex was 0.10 second. In addition, there was a ventricular premature contraction in Lead I, and the T waves in V_4, V_5, and V_6 were no longer inverted, but appeared isoelectric. The short P-R interval associated with the prolonged QRS resembled a Wolff-Parkinson-White syndrome except that the duration of the QRS was not sufficiently long.

This young boy without any history of antecedent heart disease had a definite bout of heart failure possibly precipitated by pulmonary infarction or a respiratory infection. There was no history suggestive of rheumatic fever, and the absence of typical murmurs and of specific chamber enlargement makes the diagnosis of rheumatic heart disease improbable. Since coronary arteriosclerotic heart disease is extremely unlikely in this age group and since there was no significant history, the Q waves seen in the electrocardiogram probably were due to the destruction and replacement of the normal muscle fibers of the heart by some process similar to that involving the peripheral muscles, and this might also have been the cause of the cardiac failure. The response to digitalis is similar to that in cases previously reported.

CASE 2.—A. T., a 41-year-old white man, began to have weakness of the lower extremities when he was 7½ years old. This weakness was progressive so that gradually he was unable to walk. Several years later, the upper extremities also became involved. He was admitted to the Montefiore Hospital twenty-one years ago. Examination at that time revealed deformities typical of progressive muscular dystrophy. The heart was not enlarged; the sounds were of good quality; there were no thrills or murmurs; the blood pressure was 110/80 mm. Hg. A muscle biopsy showed lesions typical of muscular dystrophy on histopathological examination.

In the hospital there has been progressive involvement of all the muscles below the neck. The patient had an episode of bronchopneumonia in 1947 and again early in 1950 which, on both

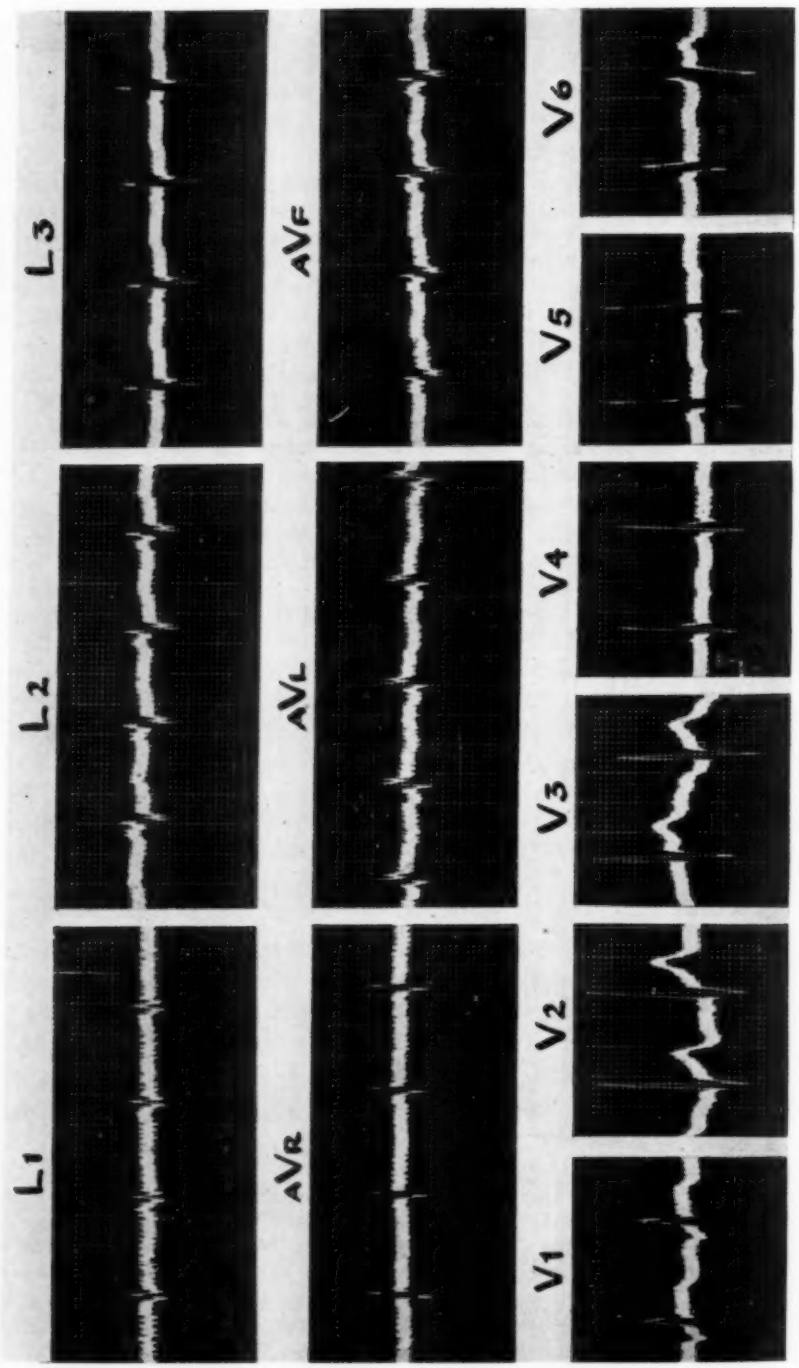

Fig. 1.

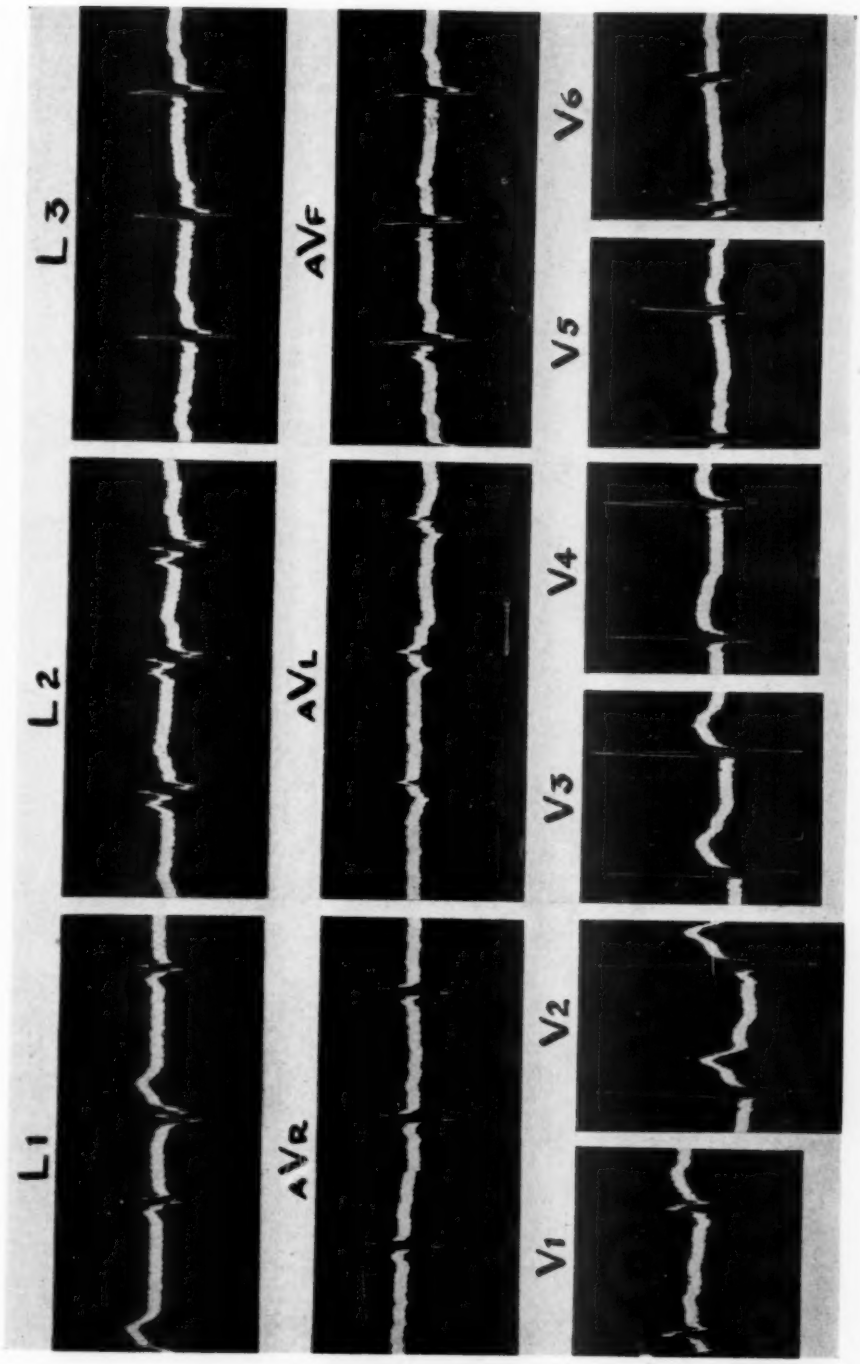

Fig. 2.

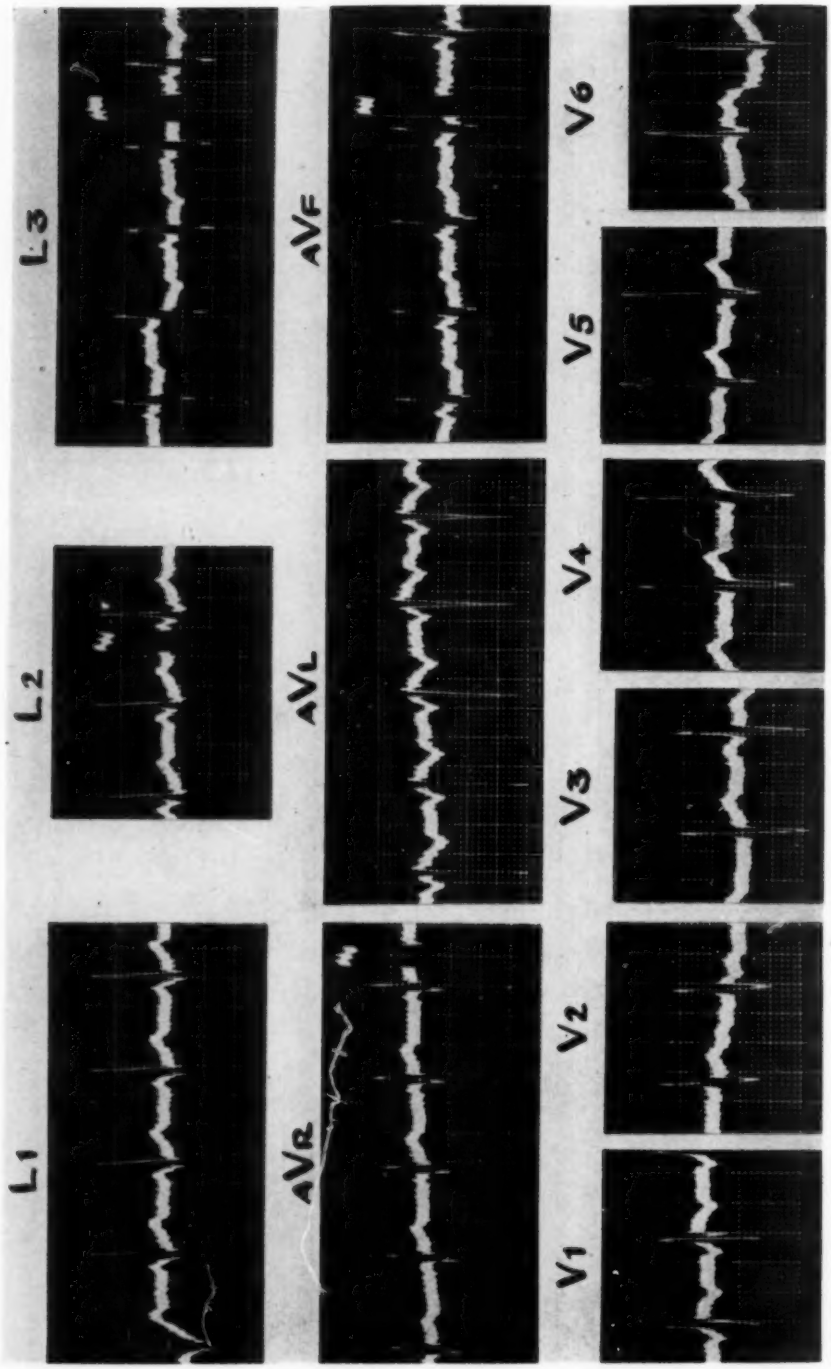

Fig. 3.

occasions, responded to antibiotic therapy. There has been no evidence of congestive heart failure, and he has never complained of precordial pain.

An electrocardiogram (Fig. 3), taken in 1950 and identical to one taken one year previously, showed a short P-R interval, 0.10 second, with a QRS complex of 0.08 second duration. There were deep Q waves in Leads I and aV_L. Subsequent exploration showed abnormal Q waves with upright P and T waves in the fourth, third, and second intercostal spaces in the V_5 position. It is possible that these Q waves signify muscular dystrophy of the cardiac musculature.

REVIEW OF CASE MATERIAL

Between 1909 and 1950, thirty-three patients with progressive muscular dystrophy were admitted to the Montefiore Hospital. There were twelve post-mortem examinations in this series. Six of the patients examined post mortem showed lesions in the cardiac muscle identical with the lesions in the skeletal muscles. The pathological findings in eleven of these cases are reported in detail by Nothacker and Netsky.[15]

Clinical findings in these patients were transient tachycardias in three and premature contractions in two. One patient, R. R., at the age of 31 years, was diagnosed at another hospital as having angina pectoris. Serial T-wave changes were reported on the electrocardiograms. At this hospital no abnormality of the electrocardiogram was noted, nor was there any clinical evidence of heart disease. Another patient, R. S. (Case 1), developed congestive heart failure.

Of the thirty-three patients, electrocardiograms were available for study in only seventeen. In five patients, the P-R interval varied from 0.10 to 0.11 second, with the ventricular rate under 100 per minute and with a QRS of normal duration; in one patient the P-R interval was questionably prolonged (0.20 second). Other findings included abnormal Q waves in two patients (Figs. 1, 2, and 3); one patient had a negative T in CF_5, but this patient had hypertension and clinical evidence of a large left ventricle; still another patient, who also had hypertension, had a diphasic T in Lead I.

DISCUSSION

It is apparent from previous studies that muscular dystrophy may involve the cardiac musculature as well as the skeletal musculature in a high percentage of instances. Our cases revealed 50 per cent involvement. If the cardiac musculature is involved, clinical and electrocardiographic manifestations logically may be expected.

Clinically, these patients fall into three catagories: (1) patients who develop congestive heart failure, (2) patients with arrhythmias or tachycardias, and (3) patients with no clinical manifestations. If a sufficient amount of cardiac muscle is involved, the remaining muscle may be inadequate to maintain sufficient cardiac output. This lack of cardiac reserve would be important at times of stress, as during pulmonary infections. Since patients with progressive muscular dystrophy are bedridden most of the time, especially later in the disease, conditions which usually help precipitate failure are absent in most of these patients. It is of interest that these patients respond to the usual methods of therapy for congestive heart failure and can be maintained for long periods on a

salt-free diet, digitalis, and mercurial diuretics. The arrhythmias and tachycardias may be due to involvement of the conduction system and the auricular musculature by the specific disease process. No studies of the auricular musculature have been made in former investigations, nor were they performed in our series. It would seem desirable to make detailed studies of the auricular musculature and conduction system in future cases with autopsy.

Electrocardiographically, no general pattern has been noted in previous studies. The reason for the short P-R interval in the electrocardiogram is not obvious, but this finding was present in a significant proportion of our patients. The short P-R interval may be related, however, to the same mechanism which leads to the arrhythmias and tachycardias.

If enough ventricular musculature is involved with progressive muscular dystrophy, the dystrophic muscle probably acts, from the electrocardiographic viewpoint, as dead muscle, and abnormally deep Q waves can appear. In two of our cases, described in detail, these abnormal Q waves were noted.

SUMMARY

1. The cardiac muscle is involved in a high percentage of cases in progressive muscular dystrophy.

2. Clinically, the vast majority of these patients show no heart disease. Some patients, however, have congestive heart failure, while others have arrhythmias and tachycardias.

3. Electrocardiographically, these patients showed short P-R intervals in five out of seventeen cases and abnormal Q waves in two cases.

REFERENCES

1. Meryon, E.: On Granular and Fatty Degeneration of the Voluntary Muscles, Med.-Clin. Tr. London **35**:73, 1852.
2. Duchenne, G. B. A.: Paraplegie hypertrophique congenitale: De l'electrisation localisle et son application a la pathologie et a la therapeutique, ed. 2, Paris, 1861, J. B. Baillière et fils.
3. Erb, W.: Ueber die "juvenile Form" der progressiven Muskelatrophie und ihre Beziehung zur sogennanten Pseudohypertrophie der Muskeln, Deutsches Arch. f. klin. Med. **34**:467, 1884.
4. Ross, J.: On a Case of Pseudo-hypertrophic Paralysis, Brit. M. J. **1**:200, 1883.
5. Marinesco, G.: Maladies des muscles, Nouv. traite de med. et de ther., 1910.
6. Goetz: Beitrag zur Atrophie muscularum lipomatosa, Aerztl. Intelligentz Bl., Munchen, 1879.
7. Sachs, B., and Brooks, H.: Progressive Muscular Dystrophy, With the Report of an Autopsy, Am. J. M. Sc. **122**:54, 1901.
8. Bunting, C. H.: Chronic Fibrous Myocarditis in Progressive Muscular Dystrophy, Am. J. M. Sc. **125**:244, 1908.
9. Potter, F. C.: A Pathologic Study of a Case of Pseudo-muscular Dystrophy With Change in the Heart Muscle, New York M. J. **90**:398, 1909.
10. Goodhart, S. P., and Globus, J. H.: On the Nature of Muscular Dystrophy With a Report on the Changes in Cardiac Muscle in Two Cases, Neurol. Bull. **1**:389, 1918.
11. Globus, J. H.: The Pathologic Findings in the Heart Muscle in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **9**:59, 1923.
12. Von Meyenberg, H.: On the Significance of Myocardial Disease in Progressive muscular Dystrophy, Schweiz. med. Wchnschr. **65**:217, 1935.

13. Cohen, S.: Myocardial Fibrosis in Progressive Muscular Dystrophy, J. Med. **17**:26, 1936.
14. Yoshida, T.: Ueber die myokardveranderung bei der progressiven muskeldystrophie, Jap. J. M. Sc., V. Path. **5**:63, 1940.
15. Hurwitz, S.: Primary Myopathies: Report of Thirty-six Cases and Review of the Literature, Arch. Neurol. & Psychiat. **36**:1294, 1936.
16. Bevans, M.: Changes in Musculature of the Gastrointestinal Tract and in the Myocardium in Progressive Muscular Dystrophy, Arch. Path. **40**:225, 1945.
17. Shank, R. E., Gilder, H., and Hoagland, C. L.: Studies on Diseases of Muscle: I. Progressive Muscular Dystrophy; A Clinical Review of Forty Cases, Arch. Neurol. & Psychiat. **52**:431, 1944.
18. Pseudohypertrophic Muscular Dystrophy; Fibrosis of Myocardium (Mass. Gen. Hosp. Case 33311), New England J. Med. **237**:163, 1947.
19. Nothacker, W. G., and Netsky, M. G.: Myocardial Lesions in Progressive Muscular Dystrophy, Arch. Path. **50**:578, 1950.
20. Boas, E. P., and Lowenberg, H.: The Heart Rate in Progressive Muscular Dystrophy, Arch. Int. Med. **47**:376, 1931.
21. Meerwein: Verhaltnisse von Herz und Zunge bei den primären Myopathien, Dissertation, Basle, 1904.
22. Berblinger, W., and Dukens, J.: I. Der kardio-intestinale Symptomenkomplex bei der progressiven Muskeldystrophie, Ztschr. f. Kinderh. **47**:1, 1929.
23. Sacara-Tulbove: Contribution a l'etude clinique de la paralysis pseudohypertrophique, Rev. de méd., Par. **14**: 1894.
24. Puddu, V., and Mussafia, A.: L'electrocardiogramme dans la dystrophie musculaire progressive, Arch. d. mal. du coeur **32**:958, 1939.
25. Schliephake, E.: II. Graphische Untersuchungen der kardio-intestinale Symtomenkomplex bei der progressiven Muskeldystrophe, Ztschr. f. Kinderh. **47**:85, 1929.
26. Salvioli, G.: The Heart in Progressive Muscular Dystrophy, Clin. pediat. **13**:53, 1931.

CARDIAC INVOLVEMENT IN PROGRESSIVE MUSCULAR DYSTROPHY

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ALTHOUGH we had been aware that instances of heart disease among dystrophic patients have been reported, the admission of a 13-year-old boy with pseudohypertrophic progressive muscular dystrophy aroused our interest in this subject again. In this patient no evidence of heart disease was found clinically, but an unusual electrocardiogram was recorded (Fig. 1). Since the usual stigmas of congenital or rheumatic heart disease were absent, it was postulated that dystrophic changes might have occurred in this patient's cardiac musculature similar to those found in skeletal muscle. In order to verify this impression, all the relevant clinical and necropsy material available to us in this hospital was reviewed. The clinical cardiac findings as well as the available histological reports form the basis of this report. A recent report from this hospital by Bevans[1] described the necropsy findings in four of our patients. One of these has been described in detail again by us because of the extensive cardiac lesions.

MATERIAL

The hospital in which this study was conducted is one for chronic diseases. We therefore had an unusual opportunity to observe this relatively rare disease. Forty-four cases of progressive muscular dystrophy were available. The men ranged from 13 to 77 years of age and the women from 18 to 65 years. These were the ages at the time of death, discharge from the hospital, or, in the instance of patients still in the hospital, at the time of the preparation of this report.

This group of patients consisted of thirty-five men and nine women. Four were Negroes. Two brothers and a sister and brother were among the patients. Of the total number, fifteen died, twelve were discharged, one was transferred to another hospital, and sixteen remained in the hospital. The duration of the illness ranged from two to sixty-five years in the men and from five to thirty-eight years in the women. Complete necropsy records were obtained on six patients who died in the hospital.

Of the forty-four patients selected for study, four were thought to have physical and laboratory findings indicative of coexisting rheumatic or arteriosclerotic heart disease (Cases 41, 42, 43, and 44). In three instances, the diagnosis of progressive muscular dystrophy was questioned, but there was enough evi-

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dence of muscular dystrophy to include these cases in the series (Cases 38, 39, and 40). One of these patients had an alternate diagnosis of amyotonia congenita, a disease classified by Batten[2] as one of the atrophic forms of muscular dystrophy. The other two cases corresponded to Batten's mixed and transitional types. In fourteen of our patients the diagnosis was confirmed by muscle biopsy and in six additional cases by autopsy.

No attempt was made to subdivide the group into the various types of progressive muscular dystophy, since it is generally believed that they comprise the same disease entity and are differentiated chiefly by those muscles which are attacked first and most severely.

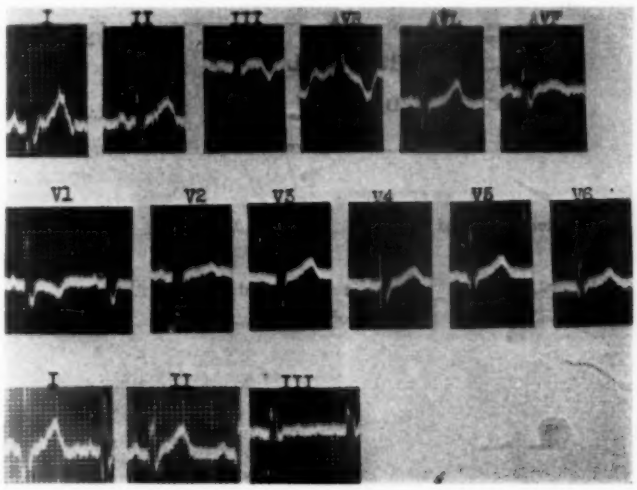

Fig. 1 (Case 2).—These electrocardiograms illustrate sinus tachycardia, tall T waves, large R wave and small S wave in Lead V_1, Q waves in Leads I and aV_L, notched QRS in aV_F, and T-wave changes in Lead III. *B* was recorded thirteen months after *A*. Leads V_1 through V_6 are one-half standardized.

Twenty-three patients, admitted to the hospital during the past ten years, had electrocardiograms recorded consisting of the three standard leads and one or more precordial leads. Eighteen patients had electrocardiograms recorded consisting of the three standard leads, the six unipolar precordial leads, and the augmented unipolar limb leads of Goldberger. Electrocardiographic studies were not done on three patients (Cases 4, 13, and 38). Teleroentgenograms of the chest were available on all the patients. The period of observation of these patients varied from three days to ten years. Follow-up of those patients discharged from the hospital was not possible.

ANALYSIS OF CLINICAL DATA

A brief clinical summary of each case including the cardiovascular findings has been included in this report.

While progressive muscular dystrophy has been primarily a disease of the younger age groups, the absence of patients in the first decade of life in our series was due to the fact that only patients over 12 years of age have been admitted

to this hospital. Onset of the disease occurred before the age of 10 years in twenty-five of the forty-four patients. Dystrophy in the other nineteen patients became manifest in the second to fifth decades. The ratio of men to women in our series was approximately 4:1, that of white to Negroes approximately 10:1.

The duration of the illness at the time of publication was under twenty years in thirty-two of the forty patients without coexistent nondystrophic cardiac disease. Of the thirteen patients who died, eleven had been ill for twenty years or less. The average duration of illness at the time of death was fifteen years, and the average age at death was 32.7 years. Four deaths were due primarily to cardiac failure. If the two deaths in patients with known rheumatic heart disease were included, six of fifteen deaths were due to cardiac failure. Thus, cardiac disturbances have played an important role in the terminal phase of progressive muscular dystrophy, particularly in younger patients. This was emphasized by Globus[3] in his report. Three patients died suddenly. It was probable that these deaths were due to cardiac disease, but unfortunately necropsies were not obtained.

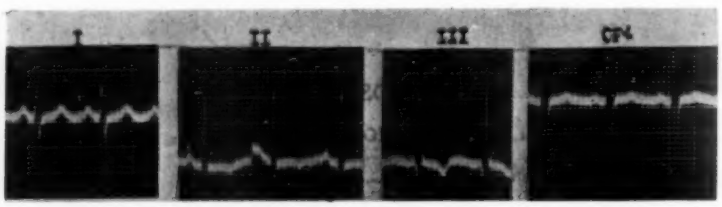

Fig. 2 (Case 5).—This electrocardiogram illustrates sinus tachycardia, inversion of T_2 and T_3, and high QRS voltage in the precordial lead CF_4. Lead CF_4 is one-half standardized (autopsy case).

About 85 per cent of the patients had some clinical manifestation of dysfunction in the cardiovascular system, and 80 per cent had abnormalities of the electrocardiogram. Among all the unusual cardiac data recorded, that obtained from the electrocardiograms apparently gave the earliest and most frequent indication of some pathological change. The most common single abnormality was the occurrence of tachycardia, present in 50 per cent of the patients. Seven patients had tachycardia in the form of paroxysms.

Unusual findings as determined by physical or radiological examination were elicited in 35 per cent of the patients, although none of the individual findings occurred with significant frequency. In three of the four cases in which death was due to cardiac failure (Cases 5, 9, 12, and 20), little indication of cardiovascular dysfunction was present until shortly before the terminal episode. In the entire series of forty patients, only one was treated for congestive failure for as long as a two-year period, while another had received digitalis in an attempt to halt bouts of paroxysmal auricular tachycardia. Both patients died of intercurrent pneumonic infections complicated by congestive failure.

Since many unusual electrocardiograms were recorded, some of these have been reproduced to indicate the variations encountered (Figs. 1 to 6). It is of interest that five of the six patients examined post mortem exhibited abnormal electrocardiograms during life. In the sixth, no electrocardiographic record was available.

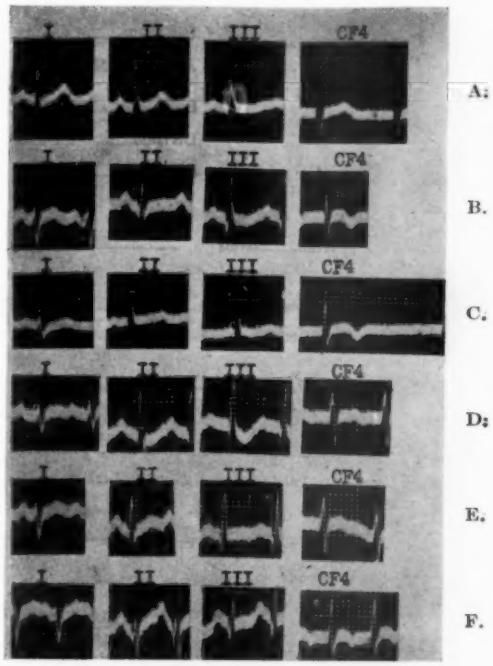

Fig. 3 (Case 11).—These electrocardiograms illustrate the serial changes over a period of one year. Tracing *B* is four months after *A* and was taken during a febrile episode. *C* is two days later, after the patient had received 0.8 Gm. of digitalis leaf. *D* is five months later, while the patient was still receiving digitalis. *E* and *F* are one and two months later, respectively, and were taken when the patient was no longer receiving digitalis therapy. CF_4 is one-half standardized in all tracings. Note the frequency of tachycardia and the increasing shift to right axis deviation (autopsy case).

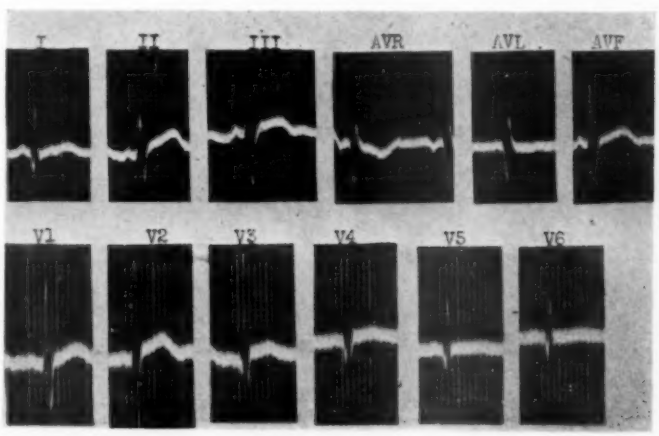

Fig. 4 (Case 14).—This electrocardiogram demonstrates a Q wave in Lead I, RS-T segment elevation in Leads II and III, and an R wave present in aV_R with aV_R and aV_L similarity. High R waves in Leads V_1 and V_2 with RS-T segment elevation in Leads V_1 through V_4 are noted. The precordial leads suggest counterclockwise rotation and high voltage. Leads V_1 through V_6 are one-half standardized.

NECROPSY DATA

Six of the fifteen patients who died were examined post mortem. As previously noted, the pathological histology of four of our cases (Cases 5, 11, 13, and 15) has been the subject of a previous report by Bevans.[1] Since the abnormal cardiac histology in all six patients examined was very similar, the findings of Case 5 only have been described again in detail in order to emphasize the striking cardiac abnormalities.

CASE 5.—

Gross Description.—The body was that of a poorly developed, but well-nourished, adolescent white boy about 15 years of age. There were contractures of the tendons of the lower extremities

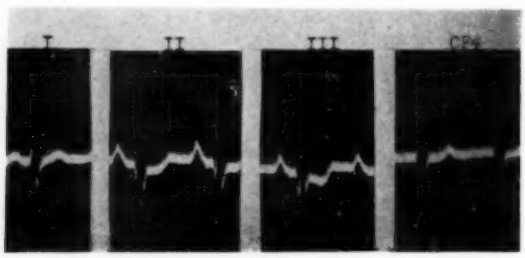

Fig. 5 (Case 15).—This electrocardiogram shows sinus tachycardia, right axis deviation, high voltage, and abnormal P waves. The RS-T segment depression represents digitalis effect. CF_4 is one-half standardized. Post-mortem examination of the auricular muscle revealed dystrophic changes.

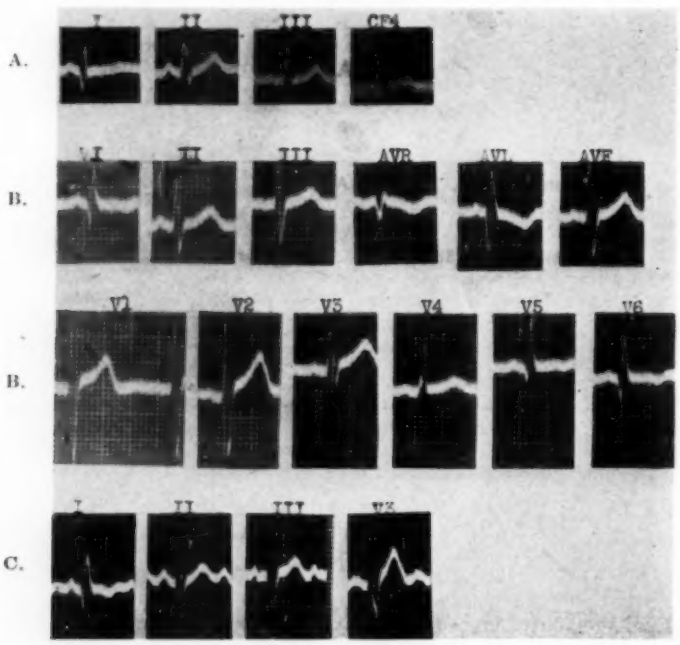

Fig. 6 (Case 18).—These serial electrocardiograms demonstrate the appearance of Q_1T_1 patterns and left axis deviation. There is a deep Q and an inverted T wave in aV_L and Q waves and inverted T waves in Leads V_5 and V_6. RS-T segments are elevated in Leads V_1 through V_3, and there are tall R waves in these leads. These changes are suggestive of an anterolateral wall myocardial infarction. *B* was recorded four years after *A* and *C* two months after *B*.

with resultant deformities. The musculature of the shoulder girdle, arms, hips, thighs, and lower extremities was noticeably atrophic.

Chest: The chest was asymmetrical because of a marked right scoliosis of the spine causing bulging of the anterior ribs on this side. The intercostal muscles were somewhat atrophic but sufficiently dense to cover the underlying pleura. When sectioned, these muscles were seen to contain a large amount of fat. The pectoral muscles were also atrophic and fatty. The heart was more centrally placed than usual. The left pleural cavity contained about 100 c.c. of clear amber fluid and the right pleural cavity about 200 c.c.

Lungs: The lungs weighed 500 grams. The pleura was transparent and the alveolar pattern regular. On section both lungs presented the same picture. Large amounts of frothy fluid exuded from all surfaces, and the bronchi were filled with the same material. The pulmonary vessels were free of thrombi and atheromatous changes.

Heart: The heart weighed 160 grams. The epicardial surfaces were smooth and glistening with an increase of epicardial fat. The endocardial surfaces of the auricles were smooth and glistening, and all the valves and supporting structures were normal. The right ventricle was dilated, and the pericardial fat was seen to invade the myocardium so that in one area no muscle could be discerned between the epicardium and endocardium. The endocardial surfaces of both the right and left ventricles were diffusely gray white in color and appeared thickened. The right ventricle measured 0.1 cm. in thickness in contrast to the left which measured 1.0 cm. Multiple sections through the myocardium of the left ventricles revealed several areas of gray-white streaking and a few areas of yellow fat deposits. The left coronary artery contained a few atheromatous plaques. The caliber of the aorta was exceedingly small throughout its course.

Abdomen: The panniculus measured about 3 cm. in thickness. The musculature had almost completely disappeared with only a few recognizable muscle fibers present between the anterior and posterior rectus sheaths. The diaphragms were thin and atrophic, with a large amount of fatty replacement.

The head, neck, brain, thyroid gland, parathyroid glands, gastrointestinal tract, liver and biliary tract, pancreas, spleen, genitourinary tract, and endocrine glands were normal in appearance.

Microscopic Description.—

Heart: A section from the posterior aspect of the left ventricle revealed the following: Over the epicardial surface there was a thick band of fibrous tissue which extended down to surround the larger blood vessels in the epicardial fat. The fat was reduced in amount, and a few lymphocytes were present. The myocardial fibers were small and fragmented. The perivascular fat was abundant, but each vessel was surrounded with a border of dense, partially hyalinized connective tissue. There was one elliptical area surrounding a vessel where only two or three fat cells persisted, and the rest of the area was composed of edematous fibrous tissue and a few wandering cells. With phosphotungstic acid and trichrome stains, no further information was obtained except that the cross striations were plainly visible. The lumina of the coronary vessels were intact.

Sections from the interventricular septum exhibited slightly edematous endocardium. The Purkinje fibers appeared even larger and paler than usual, but the cross striations were maintained. The fibrils were so spread apart that the individual fibrils were readily distinguished. The perivascular fibrosis was striking and enveloped the accompanying nerve fibers.

A section from the right ventricle taken near the apex revealed only strands of myocardial tissue persisting in abundant fat. These fibers were atrophic and slender, and a loss of their cross striations was noticeable. The blood vessels exhibited the same perivascular fibrosis as described before. Phosphotungstic acid and trichrome stains of the right ventricle exhibited more connective tissue penetrating the muscle fibers along with the fat than was realized with the usual stains.

Aorta: There was slight atheromatous thickening of the intima. The media was intact, and the vasa vasorum were not unusual.

Lungs: The interlobular septa were edematous, but the alveolar septa were thin and delicate and the spaces were small and uniform. The capillaries were greatly congested and the

perivascular connective tissue was edematous and dense. There was little edema fluid in the alveolar spaces as compared to the amount found on gross inspection of the lungs. The smooth muscles in the walls of the bronchi were wavy and shared in the generalized edema. Clumps of bacteria without cellular reaction were seen in or near the bronchi.

Stomach: A section from the central region exhibited well-preserved mucosa with large lymph follicles. The muscularis mucosae was almost destroyed and was infiltrated with lymphocytes from the mucosa. The muscularis was edematous, and there was an increase of fibrous tissue which seemed to penetrate from the serosal surface. It was interesting to note that the outer layer appeared thinned and the muscle fibers wavy and deranged. In a few areas the muscle fibers had been replaced by fibrous tissue. This change was comparable to that seen in striated muscle.

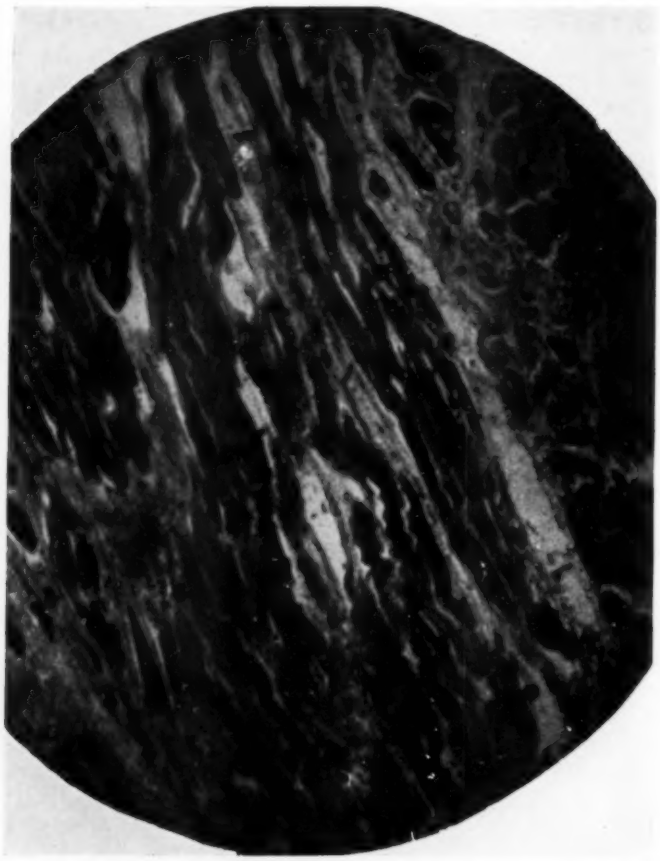

Fig. 7 (Case 5).—This photomicrograph illustrates the marked derangement of the cardiac musculature with areas of myomalacia, fat infiltration, and cellular debris (×300).

Rectum: In the lower layers of the mucosa and the upper submucosa infiltrations of polymorphonuclear cells, lymphocytes, and wandering cells were noted. The submucosa was edematous. Scarcely anything remained of the muscularis mucosae, and, with the trichrome stain, only small fragments of muscle cells could be distinguished. The fibers of the muscularis were deranged and fragmented. In these sections the changes appeared to be more severe than in any other part of the gastrointestinal tract.

Diaphragm: The muscle fibers varied in size, some being small and atrophic, others large. In many muscle fibers cross striations were well preserved. In some areas, small capillaries were surrounded by lymphocytes and wandering cells. In many areas the sarcolemma nuclei were confluent due to the disappearance of the muscle bundle. All vessels were surrounded by a band

of hyalinized fibrous tissue. With fat stains, masses of small finely divided droplets were seen within the muscle. With phosphotungstic acid and trichrome stains, striations and increased amounts of fibrous tissue were well seen.

Skeletal muscle: Sections of the intercostal, rectus, and pectoral muscles exhibited varying degreees of muscular degeneration. There was extensive fatty replacement so that the pectoral muscle section was composed of only fat with stripes of coarse connective tissue traversing it.

The gross appearance of all six hearts was similar at necropsy except in two instances. These, as noted in the case histories, were the hearts from individuals who had been subjected to the usual changes of rheumatic valvulitis and myocarditis. The hearts from these individuals were grossly larger as was to be expected. However, when the histological sections were examined, the stigmas of muscular dystrophy were readily discernible from those caused by superimposed rheumatic infections. The dual etiology of the heart disease in these individuals undoubtedly was responsible for the coexisting hypertrophy and atrophy in the same heart. A third heart, not involved by rheumatic infection, was also found to be hypertrophied (Case 15). Neither cardiac atrophy nor hypertrophy found at autopsy could be correlated with the duration of the disease or the presence of heart failure during life.

Histological examination of the hearts uniformly revealed an increase in connective tissue which, by special stain, in some instances involved nerve endings. Muscle cells were notably atrophic, and fatty replacement was common, especially in the right ventricles. Hypertrophy or swelling of some of the muscle fibers was also noted. Loss of striation of muscle cells was frequently observed. Collections of lymphocytes and wandering cells were found near blood vessels and in areas replaced by connective tissue. The similarity of the histopathology in sections from the hearts, pectoral muscles, diaphragms, stomach and rectum in one instance, and skeletal muscle biopsies was notable. Coronary artery disease of any significance was not noted in these hearts.

An excellent pathological description of the heart in progressive muscular dystrophy by Nothacker and Netsky[4] has recently appeared. It is worthy of review by those interested in this subject.

DISCUSSION

Since a historical review of the literature relative to this subject has been adequately presented by Rubin and Buchberg,[5] further reference to the older literature has been deliberately omitted in this discussion. However, it should be noted that although the presence of histological cardiac lesions has been acknowledged, clinical dystrophic heart disease has remained a questionable entity. In support of its existence there have been the reports of cardiac enlargement, disturbances of rhythm, tachycardia, especially in paroxysms, cardiac murmurs, and electrocardiographic changes of various types. From our necropsy records and clinical observations, little doubt remains concerning cardiac involvement by the dystrophic process.

We believe this is one of the first reports to describe a large number of patients on whom extensive electrocardiographic records were obtained. Some of the electrocardiographic data in our series warrant further comment because of the frequency of certain peculiarities.

Of special interest in our records was the high incidence of tachycardia and of abnormal P waves. In young patients with these findings, the diagnosis of rheumatic heart disease had to be entertained in the differential diagnosis. For example, an equivocal history of rheumatic fever was obtained in Case 42. Elevated sedimentation rates were noted on several occasions, and murmurs consistent with rheumatic heart disease were present. The other patient with rheumatic heart disease, Case 41, had a blowing apical systolic murmur, an accentuated second pulmonic sound, and a "mitral and aortic configuration" of the enlarged heart on his teleroentgenogram. The presence of rheumatic heart disease, however, did not preclude concomitant dystrophic heart disease in these patients. As for the P-wave changes, the effect of intercurrent pulmonary disease, which was common in these patients, must be considered. The absence at necropsy of pulmonary parenchymatous changes, as well as the absence of stigmas of pulmonary hypertension, precluded this interpretation in the majority of cases. Unfortunately, in only one of our autopsied patients were microscopic sections of the auricles available. In this instance, the auricular musculature was involved by the dystrophic process and may have contributed to the P-wave changes noted on the electrocardiogram (Case 15, Fig. 5).

Abnormalities of the electrocardiogram due to congenital heart disease and heart disease due to chest deformity (cor pulmonale or kyphoscoliotic heart disease) were considered because of the young age group and the high percentage of spinal and chest deformities present in our patients. The evidence cited previously again failed to implicate either as etiological in any instance. In Case 5, the diagnosis of congenital heart disease was considered, but post-mortem examination revaled the presence of dystrophic heart disease. Similarly, Case 11 had dystrophic heart disease at necropsy, although heart disease due to severe chest deformity was seriously considered during life. Furthermore, when congestive failure occurred in our patients, left-sided failure was predominant, not right-sided failure which one would expect in cor pulmonale.

Of great interest to us in the electrocardiograms was the presence of tall R waves in Leads V_1 and V_2 in thirteen of the eighteen patients with complete precordial records. Since most of the patients from whom these records were obtained had no associated chest deformity or abnormality of the teleroentgenogram, either unusual electrical rotation of the heart or increased potential derived from the right ventricle may have caused these changes. In six of the thirteen patients, Leads aV_R and aV_L were very similar, probably indicative again of some peculiar cardiac positional disturbance.

Other electrocardiographic observations were generally consistent with various degrees of nonspecific myocardial involvement. Except for high voltage R waves in V_1 and V_2 and the similarity of Leads aV_R and aV_L, there was nothing characteristic of the electrocardiograms in progressive muscular dystrophy.

SUMMARY

1. Forty-four patients with muscular dystrophy have been described. In general, no relationship between the duration and severity of the skeletal muscular lesions and those of the heart was noted.

2. The necropsy data from one of the six patients on whom histological data were available have been described in detail. The similarity of cardiac and skeletal muscle lesions was noteworthy in all our cases.

3. Variations in the electrocardiogram suggestive of abnormality were frequent. Tachycardia, abnormalities of the P waves, and tall R waves in V_1 and V_2 occurred frequently. Although no specific pattern was indicative of dystrophic involvement of the heart, patients with progressive muscular dystrophy on whom unusual electrocardiograms have been obtained should be suspected of having dystrophic heart disease.

4. In patients on whom the diagnosis of progressive muscular dystrophy (pseudohypertrophic or otherwise) has been made, the etiological diagnosis of "possible dystrophic heart disease" must always be considered. By "dystrophic heart disease" it is inferred that the heart has been pathologically involved by a histological process pathognomonic of the skeletal muscular disease.

CLINICAL SUMMARIES

CASE 1.—F. P., a 13-year-old white boy, had pseudohypertrophic progressive muscular dystrophy of seven years' duration. There were no symptoms of cardiovascular disease. The heart rate was 115 per minute, and there was a regular sinus rhythm. A questionable apical systolic murmur was said to be present. Chest and spinal deformities were absent. The electrocardiogram revealed sinus tachycardia, right axis deviation, peaking of the P wave in Lead II, broad P wave in V_2, W-shaped QRS complexes with very deep Q waves in all three standard leads and in V_5, inversion of the T wave in standard lead III, and a very tall R wave and no S wave in V_2. The patient was discharged one month after admission.

CASE 2.—J. S., a 13-year-old white boy, had pseudohypertrophic progressive muscular dystrophy of seven years' duration. The diagnosis was confirmed by muscle biopsy. There were no signs or symptoms of cardiovascular disease or kyphoscoliosis. The heart rate was 110 to 120 and the rhythm regular. The electrocardiogram revealed a wandering pacemaker with tachycardia, no axis deviation, a semihorizontal heart, significantly deep Q waves in Lead I and in aV_L, and a very tall R wave with a small S wave in V_1. The patient was still hospitalized at the time of this report.

CASE 3.—G. P., a 14-year-old white boy, had progressive muscular dystrophy of eight years' duration without any evidence of cardiovascular disturbance. Lumbar scoliosis to the left was present. The electrocardiogram revealed a sinus arrhythmia, right axis deviation, indeterminate position, peaked P wave in standard lead II, deep Q waves in Leads II and III, similarity of augmented unipolar limb leads aV_R and aV_L, high R and small notched S waves in V_1, very low voltage of the QRS complexes in V_4 through V_6, and RS-T segment elevation in precordial leads V_2 and V_3. The patient was still hospitalized at the time of this report.

CASE 4.—A. U., a 15-year-old white boy, suffered from muscular dystrophy from the age of 9 years. There were no cardiac abnormalities or spinal deformities. The heart rate was 80 per minute and the rhythm regular. He was discharged after several years of hospitalization.

CASE 5.—M. S., a 15-year-old white boy with progressive muscular dystrophy of eleven years' duration, had developed a severe dorsal scoliosis to the right so that the right side of the chest was deeper and wider than the left. There were never any signs or symptoms of cardiovascular disorder until several weeks before death when sinus tachycardia was noted and a harsh systolic murmur and thrill in the second intercostal space to the left of the sternum were found to be present. There was no cyanosis, edema, orthopnea, or dyspnea at this time. The electrocardiogram exhibited sinus tachycardia, normal axis deviation, and inversion of the T waves in Leads II and III. Chest roentgenograms showed the lungs to be clear. The cardiac configuration was not clear because of the chest deformity. At this time it was thought that the patient might have congenital heart disease with either an interventricular septal defect or a patent ductus arteriosus. How-

ever, one evening he suffered a sudden collapse characterized by cyanosis, cold clammy skin, apprehension, and frothing at the mouth. The heart and pulse rates were 180 per minute and the rhythm was regular. Only a few râles were heard in the lungs. Despite oxygen inhalation and morphine sulfate subcutaneously, the patient died within an hour. Post-mortem findings have been discussed in the text.

CASE 6.—R. G., a 16-year-old white boy, developed the first symptoms of muscular dystrophy at about 3 years of age. There were no symptoms of cardiac failure, and examination revealed normal findings except for a persistent sinus tachycardia ranging between 112 and 132 per minute. A mild dorsal kyphosis had developed. Several electrocardiograms taken over a three-year period were similar, revealing sinus tachycardia, normal axis deviation, high voltage in the standard, precordial, and augmented unipolar limb leads, and vertical position of the heart. There was persistent elevation of the RS-T segments in V_2 through V_4. The tall R waves in Leads V_1 and V_2 probably were due to counterclockwise rotation of the heart. The patient was still hospitalized at the time of this report.

CASE 7.—J. M., a 16-year-old white boy, had progressive muscular dystrophy of fourteen years' duration. The diagnosis was confirmed by muscle biopsy. During six years of hospitalization tachycardia of 110 to 118 per minute was recorded. The heart was described as normal until one month prior to death when an observer described it as enlarged to the right and left on physical examination. There was a left dorsolumbar kyphoscoliosis. An electrocardiogram taken one month prior to death revealed sinus tachycardia, low voltage of the QRS complexes in the standard leads, a significantly deep Q in Lead I, high voltage of the QRS complex in precordial lead CF_4 with elevation of the RS-T segment, and very tall T waves in the same lead. During hospitalization, there had been numerous episodes of aspiration, atelectasis, and pneumonia, and the patient finally died after several recurrent attacks of aspiration.

CASE 8.—P. R., a 16-year-old white boy, had the onset of muscular dystrophy at the age of 14 years. The diagnosis was confirmed by muscle biopsy and electrical studies. There were no symptoms or findings of cardiac dysfunction or spinal deformity. The electrocardiogram was within normal limits. The patient was discharged from the hospital several months after admission.

CASE 9.—J. V. was a 17-year-old white boy who developed progressive muscular dystrophy at 7 years of age. During his four-year hospital course, there were several episodes of dyspnea, cyanosis, râles, and low-grade fever; at least one episode was pneumonic in nature. The pulse rate on the average was 120 per minute. The heart was not enlarged, and there were no murmurs. The heart tones, however, were frequently distant, and P_2 was accentuated. Because of these findings and because of the episodes described, some observers suggested that the patient might have active rheumatic heart disease or, more likely, heart disease due to dystrophic involvement of the cardiac musculature. A dorsolumbar scoliosis to the left was present. Several electrocardiograms revealed a sinus tachycardia and a persistent deep Q and small slurred R wave in Lead I. Terminally, there were râles at the right base and a tachycardia of 150 per minute. The patient was believed to have died in acute cardiac failure. No autopsy was obtained.

CASE 10.—P. B., a 17-year-old Puerto Rican boy, had muscular dystrophy of eleven years' duration. There were no symptoms of cardiac failure. The pulse rate ranged between 84 and 136 per minute, and the cardiac rhythm was regular. The heart was shifted to the right by the marked scoliosis present, but it was otherwise normal. On the first electrocardiogram, sinus tachycardia, normal axis deviation, and a vertical position of the heart were noted. Extremely tall, peaked P waves were present in standard leads I and II and in aV_F. High voltage of the QRS complexes in Leads II and III and in V_2 and aV_F was noted. Depression of the RS-T segment in Leads II and III and in aV_F and prominent R waves in precordial leads V_1 and V_2 with diminution of the R wave as V_6 was approached were also noted. On another record obtained six months later, the following changes had occurred: right axis deviation, broad and notched, instead of peaked, P waves, Q-T intervals prolonged in Leads II and III, elevation of RS-T segment in precordial leads V_1 through V_6, inversion of the previously upright T in aV_L, and reversion of the previously inverted T wave in aV_F to the upright position. The patient has remained in the hospital.

CASE 11.—A. S. was a 17-year-old Negro boy who had dystrophy of nine years' duration. During his one year of hospitalization, there were numerous bouts of pneumonia, usually secondary to aspiration. During these episodes he was digitalized because of impending cardiac failure and tachycardia which accompanied the febrile state. However, there were also several episodes of paroxysmal tachycardia unrelated to temperature elevation. These did not respond to carotid sinus or eyeball pressure, but did respond to digitalis therapy. The heart appeared to be normal in size, although the chest was flattened in the anteroposterior diameter, and there was a right kyphoscoliosis. Serial electrocardiograms revealed the progressive development of right axis deviation and the development of peaked and notched P waves in standard leads II and III and of deep Q waves and slurred QRS complexes in the same leads. The patient died during an intercurrent pulmonary infection. A diagnosis of heart disease due to chest deformity had been made ante mortem. At necropsy, and with the aid of histological sections, it was ascertained that the myocardium, skeletal muscle, and gastrointestinal tract were involved by the dystrophic process. In addition, there were chest asymmetry and diffuse lipoid pneumonia.

CASE 12.—A. O., an 18-year-old white boy, suffered from progressive muscular dystrophy for eleven years. The diagnosis was confirmed by muscle biopsy. During his three-year observation period in the hospital there was nothing abnormal in the cardiac status except for a persistent tachycardia of 100 to 110 per minute. Kyphoscoliosis to the left was present resulting in displacement of the heart to the left. A routine electrocardiogram taken early in the hospital course revealed sinus arrhythmia and tachycardia, right axis deviation, peaking of the P wave in standard leads I and II, slurring of the R waves in the same leads, and an inverted T wave in Lead CF_4. One day before death, the patient suddenly developed tachycardia of 140 to 195 per minute with regular rhythm. The electrocardiogram at this time exhibited the following changes: no axis deviation, a small Q wave and inversion of the T wave in Lead I, splintered R wave in Lead III, and a deep Q wave and deeply inverted T wave in CF_4. There was low voltage in all the standard leads. No etiological diagnosis concerning the type of heart disease present in this patient was made. Autopsy permission could not be obtained.

CASE 13.—F. S. was an 18-year-old white boy who had had pseudohypertrophic progressive muscular dystrophy since the age of 5 years. During his five months of hospitalization there was no evidence of cardiac abnormality. A left scoliosis and a lumbar lordosis were present. After several bouts of abdominal pain, perforation of the stomach occurred, followed by peritonitis. Despite adequate surgical intervention, the patient died on the fourth postoperative day. Postmortem examination revealed, in addition to the generalized peritonitis, stigmas of progressive muscular dystrophy in the heart and stomach as well as in the skeletal muscle. Bilateral pleural effusions and moderate pulmonary edema were also present. No electrocardiograms had been obtained ante mortem.

CASE 14.—A. F. was a 19-year-old Negro man with progressive muscular dystrophy of twelve years' duration. Severe left dorsolumbar scoliosis, protrusion of the right side of the chest, and flattening of the left side of the chest were prominent. Because of these changes, the heart was displaced to the right, but physical examination of the heart was otherwise normal. The electrocardiogram revealed a deep Q wave in Lead I, elevation of the RS-T segments in Leads II and III, tall R waves in Leads V_1 and V_2, elevation of the RS-T segments in Leads V_1 through V_4, flat T waves in Leads V_5 and V_6, high voltage in the precordial leads, and a deep Q wave and a flat T wave in aV_L. The patient has remained in the hospital.

CASE 15.—E. L., a 21-year-old white man, had muscular dystrophy of seventeen years' duration. There were no symptoms of cardiac failure until the age of 19 years, when the patient developed dyspnea, orthopnea, dependent edema, and râles at the lung bases. All of these cleared with digitalization, which the patient required for the remaining two years of his life. The blood pressure varied from 80/60 to 125/100 mm. Hg and the pulse rate from 90 to 120 per minute. The heart was enlarged and had a "mitral configuration" by roentgenogram. About one year prior to death, a diastolic apical gallop was first heard and was present thereafter. Ten months before death, a systolic apical murmur was heard, the second pulmonic sound became accentuated, and the second aortic sound was faint. An electrocardiogram seven months before death revealed a sinus tachycardia, digitalis effect, a broad notched P wave in Lead I, and peaked P waves in

Leads II and III. It was believed that the patient was suffering either from rheumatic heart disease or dystrophic heart disease. Death resulted from an intercurrent pulmonary infection. Post-mortem examination revealed the changes of progressive muscular dystrophy in the myocardium. The pneumonia proved to be of the aspiration type. In this instance, since the heart was larger than normal, heart failure, chronic pneumonitis, and myomalacia, with secondary cardiac enlargement, were probably contributory to death.

CASE 16.—C. S., a 23-year-old white man, had suffered from the effects of pseudohypertrophic muscular dystrophy since the age of 6 years. He did not present any symptoms of cardiac dysfunction. There was marked chest deformity with lumbar lordosis, loss of the dorsal curve, and increased anteroposterior diameter of the chest. The heart was displaced to the right as a result of these changes. The electrocardiogram exhibited these interesting changes: In Leads I and II notched P waves and high voltage QRS complexes were present; augmented unipolar limb leads aV_L and aV_R were similar, and high voltage was present in aV_F; there was RS-T segment elevation in aV_F; tall R waves were present in V_1 and V_2. This patient has remained in the hospital.

CASE 17.—B. S., a 23-year-old white man with pseudohypertrophic muscular dystrophy of eighteen years' duration, also had diabetes mellitus for at least ten years. The cardiovascular system was normal on clinical examination. Of interest in the electrocardiogram were deep Q waves in Leads II and III and in aV_F, moderately tall R waves in V_1 and V_2, and RS-T segment elevation in V_2 and V_3. He was discharged from the hospital.

CASE 18.—S. G., a 24-year-old white man, had had progressive muscular dystrophy since early infancy. There were no complaints referable to the cardiovascular system, but the pulse rate was noted to be very labile clinically. Heart sounds were distant. The chest was deformed due to a funnel depression beneath the sternum, mild scoliosis and lordosis, and protrusion of the left chest anteriorly. In the serial electrocardiograms the following were noted: (1) a deep Q wave and flat T wave in Lead I, splintered QRS complexes in Leads II and III and in CF_4; (2) four years later, inverted T waves in Lead I, deep S waves in Leads II and III without splintering of the QRS complexes, a deep Q wave and inverted T wave in aV_L, tall R waves in V_1 and V_2, RS-T segment elevation in V_1 through V_3, notched R waves in V_3 and V_4, deep Q wave and inverted T wave in V_5 and V_6; (3) two months later, a definite left axis deviation and sinus tachycardia. The electrocardiograms resembled those of an old anterior wall myocardial infarction. This patient remained in the hospital.

CASE 19.—S. I. was a 24-year-old white man who had been ill with progressive muscular dystrophy for at least ten years. Physical findings referable to the heart were normal, and there was no deformity of the spine or chest. The first electrocardiogram revealed a sinus tachycardia, high voltage of the QRS complexes in Leads II and III, and some broadening of the P wave in Lead II. Five years later, there were ventricular premature contractions and high voltage in standard, unipolar limb, and precordial leads. In addition, a W-shaped QRS complex with a flat T wave was now present in Lead I. The patient has remained in the hospital.

CASE 20.—J. P. was a 26-year-old white man with progressive muscular dystrophy present since the age of 8 years. The diagnosis was confirmed by muscle biopsy. The chest was emphysematous with dorsolumbar lordosis and scoliosis to the right, but the heart sounds were always described as of good quality. Three weeks before death, the patient complained of dyspnea and coughed up frothy white sputum. This was accompanied by low-grade fever. Heart sounds now were of poor quality with a tic-tac rhythm. There were physical findings suggestive of right pleural effusion with underlying pneumonia or atelectasis. On the day before death, pulmonary edema developed rapidly and despite rapid digitalization, oxygen, and diuretics, failure and tachycardia persisted, and the patient died the next day. Many electrocardiograms taken during the eight years of hospitalization were similar including the record taken shortly before death. In all of the records there was regular sinus rhythm, no axis deviation, a deep Q wave and flat T wave in Lead I, an M-shaped complex in Lead III, and occasional ventricular premature contractions. Necropsy was not performed.

CASE 21.—T. K., a 27-year-old white man, was known to have had pseudohypertrophic progressive muscular dystrophy for at least twenty-three years. He was under observation in

this hospital for ten years, and during the last six years he complained of occasional sharp or pressing precordial pain, related to food intake and relieved by nitroglycerin. In addition, there were several episodes of bronchitis and pneumonia, with consolidation and pleural thickening of the left lower lobe of the lung. Because of the chest pain, some observers offered the diagnosis of dystrophic heart disease with coronary insufficiency. By means of muscle biopsy, the diagnosis of pseudohypertrophic progressive muscular dystrophy was confirmed. Dorsal lordosis and scoliosis to the left were present and probably accounted for an anatomical shift of the heart to the right. Many electrocardiograms were recorded and were essentially the same, with regular sinus rhythm or sinus arrhythmia, no axis deviation, and high voltage in the standard leads, the precordial leads, and the augmented unipolar limb leads. The R waves were tall in V_1 and V_2; the RS-T segments were elevated in V_2 through V_4; aV_R and aV_L were almost identical, with vertical positioning of the electrical axis of the heart. The patient has remained in the hospital.

CASE 22.—C. G., a 33-year-old white man, had had muscular dystrophy since he was 25 years of age, manifested by muscular weakness and lumbar lordosis. Biopsy confirmed the muscular degeneration. There were no cardiac symptoms or abnormal findings except that of accentuation of the left auricular curve on fluoroscopy. There were frequent bouts of bronchitis, but otherwise the lung fields appeared to be normal. The electrocardiogram was within normal limits except for notched P waves in Leads II and III and a significantly deep Q wave and flat T wave in Lead III. The patient was discharged after fourteen months of hospitalization.

CASE 23.—J. C., a 36-year-old Negro man, had had pseudohypertrophic progressive muscular dystrophy, confirmed by muscle biopsy, for at least twenty years. He had no symptoms referable to the heart, but there was a history of several attacks of joint pain without swelling, heat, or tenderness eleven years after the onset of the dystrophy, lasting about six months. During our ten years of observation in the hospital, the blood pressure readings varied from 130 to 160/90 to 120 mm. Hg and the cardiac rate from 75 to 100 per minute. There was a persistent precordial systolic murmur, heard loudest at Erb's point, and during the years some observers had described an apical systolic murmur and accentuation of the second pulmonic sound. The heart was not enlarged, and there was no chest deformity. Diagnoses of rheumatic heart disease, or hypertensive cardiovascular disease, or dystrophic heart disease were offered at various times. Data which might confirm the first two of these diagnoses were lacking. The electrocardiogram revealed, in addition to vertical position and counterclockwise rotation, a deep Q wave and low T wave in Lead I, a deep Q wave and inverted T wave in aV_R, splintering of the QRS complexes in V_1 through V_3 with tall R waves in these leads, and marked, persistent elevation of the RS-T segments in Leads V_1 through V_5. This patient has remained in the hospital.

CASE 24.—R. A., a 39-year-old white man, suffered from progressive muscular dystrophy for at least thirty-eight years. Except for one episode of basal râles, dyspnea and tachycardia, there were no symptoms referable to the cardiovascular system. Severe scoliosis and chest deformity were present, and the heart was displaced to the right. The second pulmonic sound was accentuated. Except for tachycardia and low T waves in the standard leads, the electrocardiogram was within normal limits. The patient was discharged one year after admission.

CASE 25.—J. C., a 39-year-old white man, had suffered from progressive muscular dystrophy since the age of 13 years. By means of muscle biopsy, the diagnosis had been confirmed. There were no abnormal cardiac symptoms or findings other than distant apical heart sounds. Some lordosis and funnel deformity of the chest were noted. These changes were present on the electrocardiogram: broad, notched P waves in all standard leads, gradual development of a W-shaped QRS complex in Lead III. The patient has remained in the hospital.

CASE 26.—I. C., a 41-year-old white man, had progressive muscular dystrophy of only six years' duration. There were no cardiovascular sysmptoms. Physical examination revealed no abnormalities, but moderate pulmonary congestion was reported on the chest roentgenogram. Left dorsal scoliosis and lumbar lordosis were present. Of significance on the electrocardiogram were incomplete left bundle branch block and elevation of the RS-T segment in Lead III with a sharply inverted T wave. The patient was discharged several months after admission to the hospital with no apparent cardiac disability.

CASE 27.—M. K. was a 51-year-old white man with progressive muscular dystrophy of nineteen years' duration whose diagnosis had been confirmed by muscle biopsy. Except for a history of nocturnal ankle edema for one year prior to the onset of dystrophy, there was no previous evidence of cardiac failure. Except for a rough apical systolic murmur and distant heart sounds, physical examination of the heart was within normal limits. There was no spinal deformity. On the electrocardiogram, flat T waves in Lead I, tall T waves in Leads II and III, and high voltage of the QRS complex in Lead II were present. The T wave in CF_4 was diphasic. After seven years of hospitalization, the patient was transferred to a tuberculosis hospital because of the development of an active apical pulmonary tuberculosis.

CASE 28.—A. K., a 52-year-old white man, had suffered from progressive muscular dystrophy since the age of 24 years. No deformity of spine or chest had developed in this time. During ten years of hospitalization there was no evidence of cardiac disease. The electrocardiogram was within normal limits. He has remained in the hospital.

CASE 29.—W. F., a 54-year-old white man, developed an atypical, but severe, type of progressive muscular dystrophy at 50 years of age. Chemical, electrical, and biopsy studies of muscle confirmed this diagnosis. No spinal or chest deformity had developed in the intervening four years. During the two years of hospitalization, the patient complained of occasional palpitations followed by precordial and left shoulder pain. During one such episode, myocardial infarction was thought to have occurred, but the electrocardiogram recorded at that time failed to confirm this impression. Heart sounds in this patient were somewhat distant, and the first sound at the apex was accentuated with a blowing apical systolic murmur constantly heard. Premature contractions were frequent. The heart was not enlarged by roentgenogram. There were occasional episodes of cough and fever and a persistent incomplete consolidation at the left base, believed to be due to chronic lipoid pneumonia. He died during a flare-up of the pulmonary infection. Serial electrocardiograms during his twenty months of hospitalization revealed a regular sinus rhythm, premature auricular and ventricular contractions, progressive development of left axis deviation, a horizontal heart with clockwise rotation, and peaking and notching of the P waves in the three standard leads.

CASE 30.—P. D., a 56-year-old white man, first had symptoms of pseudohypertrophic progressive muscular dystrophy at 50 years of age. Muscle biopsy confirmed the diagnosis. There were no cardiac abnormalities, and the electrocardiogram was within normal limits. He was discharged after an uneventful hospital course.

CASE 31.—A. C., a 57-year-old white man, suffered from progressive muscular dystrophy for at least seven years. The diagnosis was established by muscle biopsy in addition to the usual clinical findings. No symptoms or signs suggestive of cardiovascular disorder were present. During his hospitalization over a five-year period, there were occasional grand mal seizures thought to be unrelated to the muscular disorder and several episodes of lobar pneumonia. A moderate kyphoscoliosis was present. The patient died during an intercurrent pulmonary infection. Because of beginning heart failure, he was digitalized shortly before death. All electrocardiograms revealed a regular sinus tachycardia, left axis deviation, diphasic T wave in Lead I, peaked P wave in Lead II, and flat or inverted T waves in Lead III and in CF_4. In addition, high voltage of the QRS complexes in Leads I and II, present on the admission electrocardiogram and suggestive of left ventricular preponderance, gradually disappeared.

CASE 32.—L. S., an 18-year-old white girl, the sister of C. S., Case 16, had suffered from pseudohypertrophic muscular dystrophy since she was 5 years of age. There was no cardiovascular history or record of rheumatic fever. Since there was a difference of opinion as to the presence of cardiac murmurs, a stethogram was recorded, and apical systolic and diastolic murmurs were noted to be present. As a result, rheumatic heart disease was thought to be present by one observer, although good clinical evidence was absent. A moderate left dorsolumbar scoliosis was present. The patient remained hospitalized. Numerous electrocardiograms recorded during the five years of hospitalization were not unusual except for persistent tachycardia and peaking of the P wave in Lead II.

CASE 33.—M. W., a 37-year-old white woman, suffered from pseudohypertrophic muscular dystrophy for at least twenty-three years. She had no chest deformity nor clinical abnormality

of the cardiovascular system. The electrocardiogram was not unusual. She was discharged to her home after observation.

CASE 34.—T. S. was a 38-year-old white woman who had noticeable muscular weakness shortly after birth. The clinical course and muscle biopsy were pathognomonic of progressive muscular dystrophy. She had no cardiac complaints and no abnormal cardiac findings. There was a dorsal scoliosis to the right. She died after several days of uncontrollable vomiting. Of interest in the electrocardiogram were notched and broad P waves in Leads I and II, a deep Q wave in Lead III, and inverted T wave in Lead CF_4.

CASE 35.—R. N., a 41-year-old woman, was observed in this hospital for only a three-week period. She had suffered from progressive muscular dystrophy for fourteen years, with no cardiovascular complaints. On examination, the heart was found to be normal except for an accentuated pulmonic second sound, but dorsolumbar kyphoscoliosis was present. An electrocardiogram recorded during an episode of irregular tachycardia revealed a sinus tachycardia with runs of irregular supraventricular tachycardia. She was discharged to her home.

CASE 36.—K. S. was a 63-year-old white woman who had had pseudohypertrophic muscular dystrophy for fifteen years. She never had any cardiac distress, although the pulse rate usually exceeded 100 beats per minute. The heart was slightly enlarged, and an aortic systolic murmur was present. No chest deformity was noted. An electrocardiogram revealed a sinus tachycardia with occasional auricular and ventricular premature contractions and slurring of the QRS complexes in all standard leads. The patient died suddenly, and autopsy permission could not be obtained. Death was attributed to arteriosclerotic heart disease with possible coronary artery thrombosis.

CASE 37.—N. K., a 65-year-old white woman with pseudohypertrophic muscular dystrophy for twenty-eight years, had no cardiac abnormalities either symptomatically or by physical findings. There was a marked lumbar lordosis and scoliosis to the left. An electrocardiogram revealed a sinus arrhythmia with auricular premature contractions, flat P and T waves in Lead I, and notched P waves in Leads II and III. After eight years of hospitalization, the patient died suddenly following two days of intermittent vomiting and abdominal pain. Autopsy was not performed.

CASE 38.—J. E., a 53-year-old white man, was observed in this hospital for only 2½ weeks. He had had progressive muscular weakness for five years and was believed to have atypical progressive muscular dystrophy. An alternate but less favored diagnosis was amyotrophic lateral sclerosis. There was a history of hypertension of eight years' duration, and blood pressure values ranged from 155 to 180/100 mm. Hg. Otherwise, cardiac findings were within normal limits. The pulse rate was regular at 90 to 100 per minute. There was no chest deformity. No electrocardiograms were recorded in this hospital. He was discharged with the diagnoses of probable atypical progressive muscular dystrophy and possible hypertensive cardiovascular disease.

CASE 39.—J. A., a 13-year-old Negro girl, had had muscular weakness all her life. The diagnosis rested between progressive muscular dystrophy and amyotonia congenita. A left scoliosis and dorsolumbar lordosis had developed. Her heart rate was noted to vary from 84 to 122 per minute. The heart was considered to be normal as determined by physical examination. Several electrocardiograms were similar illustrating sinus tachycardia and arrhythmia, deep broad Q waves and inverted T waves in Lead III, RS-T segment elevation in Lead II, and tall R waves in V_1 and V_2. She has remained in the hospital.

CASE 40.—K. F. was a 50-year-old white woman with muscular weakness of five years' duration. The diagnosis was either atypical pseudohypertrophic progressive muscular dystrophy, polyneuritis, or chronic anterior horn-cell disease. The heart was normal. The electrocardiogram revealed regular sinus rhythm, left axis deviation, and RS-T segment depression in Leads II and III. She was discharged to her home after observation.

CASE 41.—V. C., a 17-year-old white boy, suffered from pseudohypertrophic progressive muscular dystrophy for a period of twelve years. He was observed in this hospital for two years. During this period there were frequent episodes of palpitation and tachycardia with the pulse rate ranging from 90 to 150 per minute. Although there was no history of rheumatic fever, physical findings were typical of rheumatic heart disease with an apical systolic blowing murmur

and with an accentuated second pulmonic sound. The heart was enlarged both clinically and on x-ray examination, with a "mitral and aortic configuration." There was no chest or spinal deformity. Various diagnoses including rheumatic heart disease, possible dystrophic heart disease, and possible idiopathic cardiac hypertrophy were made. One electrocardiogram, taken during the middle of the hospital course, exhibited regular sinus rhythm, right axis deviation, slurred W-shaped QRS complexes in Leads I and II, and RS-T segment elevation in CF_4. The patient died in peripheral vascular collapse during an intercurrent pneumonic infection. There were hepatomegaly, cyanosis, dyspnea, tachycardia, and cold clammy extremities before death despite rapid intravenous digitalization. Post-mortem examination revealed progressive muscular dystrophy, myocardial hypertrophy, fibrosis, fatty infiltration and degeneration, chronic active rheumatic myocarditis and endocarditis, chronic passive congestion of the viscera. There was a small pericardial effusion, and the mitral valve was slightly thickened. The heart weighed 460 grams, and all chambers were dilated.

CASE 42.—V. G., a 21-year-old white man, was the brother of S. G., Case 18. He had suffered from pseudohypertrophic progressive muscular dystrophy for at least ten years and was under observation in this hospital for six years. There was an equivocal history of rheumatic fever, but on admission to this hospital the cardiovascular system was completely normal. However, during the last two years of hospitalization, right and left heart failure became evident, requiring digitalization and frequent mercurial diuretics. The heart failure became progressively more difficult to control, as did the persistent tachycardia. The erythrocyte sedimentation rate was elevated. There were episodes suggestive either of pulmonary infection or pulmonary infarcts. The chest roentgenograms revealed only cardiac enlargement, pulmonary congestion, and bilateral pleural effusions of varying degree. During this terminal period, systolic and presystolic murmurs were heard at the apex. The patient died in cardiac failure. The clinical cardiac diagnosis was probable rheumatic heart disease with mitral stenosis and insufficiency and possible dystrophic heart disease. The electrocardiogram revealed sinus tachycardia and arrhythmia, a shift from normal to right axis deviation over a three-year period, W-shaped QRS complexes and low T waves in Lead I, peaked or broad P waves and deep Q waves in Lead II, peaked, diphasic P waves in V_1, and high R waves in V_1 and V_2 which diminished as V_5 and V_6 were approached.

Post-mortem examination demonstrated bilateral pleural and pericardial effusions, recent left upper lobe pulmonary infarct, cardiac hypertrophy and dilatation with chronic rheumatic mitral valvulitis, and changes due to progressive muscular dystrophy. The skeletal muscles revealed changes pathognomonic of muscular dystrophy, and the histological findings resembled those found in the cardiac musculature.

CASE 43.—J. P., a 77-year-old white man, had suffered from progressive muscular dystrophy since the age of 12 years. For several years he had had dependent edema, prolonged circulation times, and rapid auricular fibrillation, requiring the administration of digitalis in an effort to control the heart failure. A vague history of hypertension had been obtained. The heart was found to be enlarged on examination, and a harsh apical systolic murmur and thrill were present. No chest deformity was noted. Electrocardiograms revealed auricular fibrillation. It was believed that the patient had hypertensive and arteriosclerotic cardiovascular disease, questionably rheumatic heart disease, and possibly dystrophic heart disease. He has remained in the hospital.

CASE 44.—F. L., a 59-year-old white woman, suffered from muscular dystrophy for twenty-three years. Hypertension, recurrent ankle edema, and frequent episodes of dyspnea, cyanosis, palpitations, and pain in the chest and left arm had occurred intermittently for 20 years. During her three years of hospitalization these symptoms plus hepatomegaly and basal lung râles and wheezes necessitated the use of digitalis and mercurial diuretics. The heart rate varied from 36 to 80, and the rhythm was regular. The blood pressure was 140 to 210/90 to 140 mm. Hg. The heart was enlarged, and there was an apical systolic murmur present. No chest deformity was present. On repeated electrocardiograms the following changes were noted: change from a regular sinus rhythm to a nodal rhythm, a gradual development to left ventricular preponderance pattern, prolongation of the Q-T interval. A diagnosis of hypertensive and arteriosclerotic cardiovascular disease was made, and she was discharged after three years of observation.

REFERENCES

1. Bevans, M.: Changes in Musculature of G-I Tract and Myocardium in Progressive Muscular Dystrophy, Arch. Path. **40**:225, 1945.
2. Batten, F. E.: The Myopathies or Muscular Dystrophies, Quart. J. Med. **3**:313, 1909-1910.
3. Globus, J. H.: The Pathologic Findings in Heart Muscle in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **9**:59, 1923.
4. Nothacker, W. G., and Netsky, M. G.: Myocardial Lesions in Progressive Muscular Dystrophy, Arch. Path. **50**:578, 1950.
5. Rubin, I. L., and Buchberg, A. S.: The Heart in Progressive Muscular Dystrophy, Am. Heart J. **43**:161, 1952.

HYDRAULIC FORMULA FOR THE CALCULATION OF THE CROSS-SECTIONAL AREA OF THE MITRAL VALVE DURING REGURGITATION

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THE introduction of the cardiac catheter by Cournand and Ranges[1] made available a new method for the detection of auriculoventricular valvular regurgitation in man. Bloomfield and associates[2] first reported on the altered right atrial pressure pulse in tricuspid regurgitation, while the authors[3,4] pointed out the changes in the form of the pulmonary "capillary" pressure tracing in mitral regurgitation. Except for Keys and Friedell's[5] Fick and roentgenkymographic studies of cardiac output, there have been no attempts to evaluate the quantitative aspects of valvular insufficiency. It was decided, therefore, to apply hydraulic principles to the regurgitant valve in a fashion similar to that used previously for the stenotic valve[6] in order to evaluate two unknowns: the anatomic cross-sectional area of the regurgitant valve defect and the amount of blood regurgitating through that defect.

GENERAL PRINCIPLES

Normal mitral valve closure involves constriction of the annulus fibrosus,[7] approximation of the nodular ridge and lower one-third portion of the cusps, and the tensor action of the lateral leaflets.[8]

Rheumatic disease may result in two lesions which can lead to defects of valve closure and possible regurgitation. These are (1) thickening and fusion of the valve leaflets, which can limit their coapting ability, resulting in a valve which is partly open during systole, and (2) actual absence of part of one or both leaflets, such as a shortened anterior leaflet leaving an anatomic defect when the valve cusps close with systole.[9] Whether or not regurgitation takes place depends on the ability of the various phenomena of systole to close the valvular defect. With systole, the ventricular wall moves in and buttresses the posterior leaflet. In so doing, the papillary muscles and chordae tendineae are moved across the ventricular surface of the mitral orifice. The wall itself, the papillary muscles, or thickened chordae may come into direct apposition with the valve orifice during systole and either wholly or partly occlude it.[10] Second, the rising ven-

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tricular pressure will squeeze the cusps together. Just how effective these factors are will depend on the size and spatial orientation of the valvular defect (Fig. 1). As Harken and co-workers have pointed out,[9] regurgitation usually occurs due to a defective anterior leaflet, the result being an orifice directed into the outflow tract. In this situation, neither the squeezing action of systole nor the ventricular wall and associated structures can close the defect. Similarly, when the stenotic orifice is comparatively large, even if oriented caudally, the orifice may be too big to be completely closed by ventricular wall, papillary muscle, or thickened chordae, and the leaflets may be too rigid or deformed to be perfectly approximated by ventricular pressure.[8] When the orifice is oriented posteriorly or is small and oriented caudally, however, there is the possibility that the ventricular wall may readily fill in the defects left by poor valve closure and prevent regurgitation (Fig. 1).

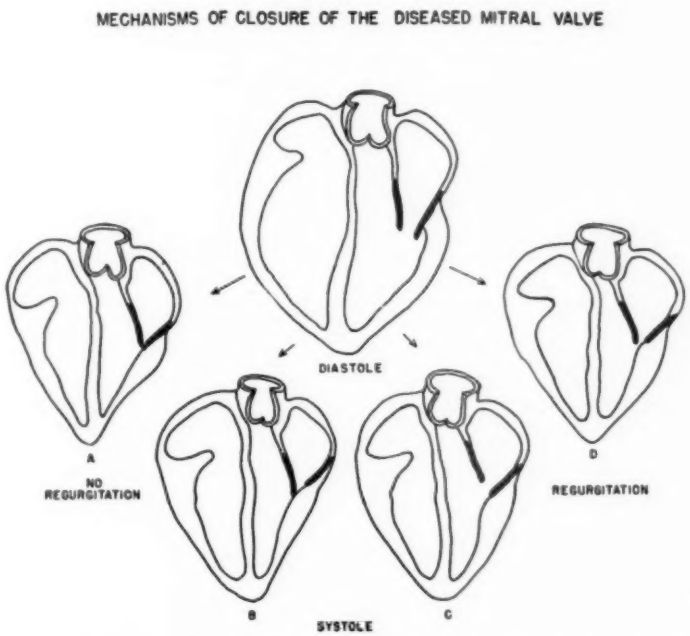

Fig. 1.—In this diagram are seen sagittal sections of the heart which portray the phases of diastole and systole. The lower four figures represent the mechanisms by which a diseased mitral valve, seen in cross section, may close during systole. In heart *A*, there is a good approximation of properly apposed leaflets so that no regurgitation occurs. In heart *B*, there is a defect of the posterior valve cusp due to rheumatic disease. No regurgitation occurs because with systole the ventricular wall, papillary muscles, or chordae tendineae become interposed with the anterior valve cusp, covering over the defect. In heart *C*, the anterior leaflet is defective, and regurgitation readily occurs because there is no other structure to fill in the gap. In heart *D*, the mitral orifice is moderately large, and the cusps are thickened but without defect. Imperfect approximation of valve leaflets occurs due to thickening and fusion. The resulting regurgitant orifice is so large that it can only be partly closed by the ventricular wall and its associated structures. (Illustration by Margaret S. Owen.)

In summary, residual deformity, orifice size and positioning, and compensation during systole for defects of valvular closure are the major factors leading to mitral regurgitation.

Through the interplay of these dynamic and anatomic factors, a definite regurgitant orifice is formed which partly protrudes into and is almost at right angles to the outflow of blood from the ventricle (Fig. 1). As systole begins, blood moves up the ventricular outflow tract and regurgitates into the left atrium. The amount of regurgitation will depend mainly on the size of the valvular defect and the hydraulic pressure exerted upon it.

HYDRAULIC ASPECTS OF MITRAL REGURGITATION

$$A = \frac{F}{c\sqrt{2g(P_1 - P_2)}}$$

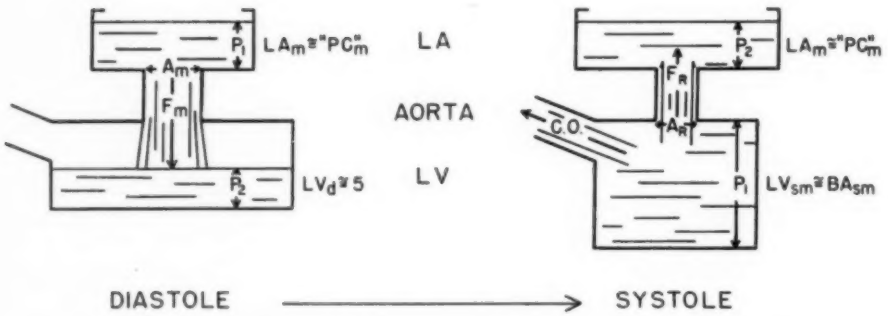

Fig. 2.—In this diagram are shown the hydraulics of mitral regurgitation. The figure to the left shows the left atrium and ventricle during diastole. The total amount of blood entering the ventricle during diastole to be expelled in systole (*Fm*) must pass through the mitral valve and is dependent on the cross-sectional area of the valve in diastole (*Am*), the pressure gradient across it (*LAm-LVd*), and the duration of diastole. This volume of blood is then expelled, as shown in the figure to the right, a portion via the aorta, the aortic output (*CO*), and the remainder regurgitating back through the mitral valve. This regurgitant blood flow (*Fr*) is dependent on the area of the regurgitant mitral orifice (A_r), the pressure gradient across it (LV_{sm}-LA_m), and the duration of systole. Further details are described in the text.

As is the case with valvular stenosis,[6] valvular regurgitation may, within limits, be analyzed hydraulically (Fig. 2). Hydraulic principles are strictly applicable only when the orifice is fixed. One can obtain little information as to whether the mitral regurgitant orifice is fixed from examination of autopsy specimens. The interrelation of valve leaflets and ventricular wall structurse during systole is important in forming the orifice. Their spatial relations are not easily simulated outside the body. It was decided, therefore, to proceed with hydraulic analysis, with the realization that the results of the analysis *per se* would indicate whether or not the orifice were really fixed. Thus, if different sets of hydraulic data on the same patient gave the same calculated regurgitant area, it would be fair to assume that the orifice was fixed and the use of hydraulic principles justified.

Another problem in hydraulic analysis is the question of streamline flow within the ventricle with its attendant effects on blood flow and pressure. The

regurgitant orifice is situated in the side wall of the outflow tract. If there is streamline flow, then the velocity of flow would result in a greater effective pressure head being applied to the aortic than to the regurgitant orifice because the aortic orifice is end-on and the regurgitant orifice at right angles to the stream. In this particular instance, however, it is not known whether or not there is streamline flow, and even if streamline flow were present, its effect would be negligible, because the velocity component of blood flow at rest comprises less than 10 per cent of the useful energy of the ventricle.[11] Therefore, the regurgitant orifice may be considered to be affected by almost the same pressure head as the aortic orifice.

An application of the hydraulic method to the study of mitral insufficiency will be described in the following sections. Equations will be presented and solved to give formulas for which data are available for making the desired calculations. An attempt has been made to derive equations which make use of the maximum number of values obtainable through a right heart catheter and arterial needle.

Before presenting the derivation of the formulas, one difference between them and the mitral stenosis formula[6] must be pointed out. With the latter, it was possible to make theoretical predictions about blood flow and pressure levels because only a single orifice was in question. In any double orifice system, however, where there are changing conditions of pressure and flow, particularly in a system where intraventricular pressure is regulated by the frictional resistance beyond one orifice, the phenomena defy exact mathematical expression with the limited empirical data now available.[12] The variables which govern the apportioning of flow and pressure head between two competing orifices are innumerable, and satisfactory theoretical predictions cannot be made about flow rate or pressure loss through one or the other orifice. The formulas to be derived are mathematically correct, but their use in hypothetical analysis is decidedly limited. They are valid, however, for solution of problems wherever the *proportionation* of blood flow between the orifices is experimentally obtained. Once this apportioning of blood is known, all other relationships may be defined with ease.

DERIVATION OF GENERAL FORMULA

Mitral Regurgitant Area (MRA).—The interrelation of pressure and blood flow across an orifice depends on the area of the orifice. Conversely, from pressure and flow data, the area may be calculated as follows[11]:

$$1.\quad A = \frac{F}{C\sqrt{2g(P_1 - P_2)}}$$

where A = area of orifice

F = rate of flow through the orifice

C = discharge coefficient

g = gravity acceleration

$P_1 - P_2$ = pressure gradient across the orifice.

In order to obtain the regurgitant area (MRA) of the mitral valve during systole, this formula may be rewritten as follows:

$$2.\quad MRA = \frac{MRF}{C \times 44.5 \sqrt{LV_{sm} - LA_m}}$$

where MRF = mitral regurgitant blood flow (c.c. per systolic second)
C = discharge coefficient
$44.5 = \sqrt{2g} = \sqrt{1960}$
LV_{sm} = left ventricular mean systolic ejection pressure (mm. Hg)
LA_m = left atrial mean pressure (mm. Hg).

By this formula it is possible to calculate the size of the mitral regurgitant orifice, provided the rate of regurgitant flow and the pressure gradient are known.

Rate of Mitral Regurgitant Flow (MRF).—Regurgitation occurs only during part of each cardiac cycle, namely ventricular systole, when ventricular pressure exceeds atrial pressure. Therefore, the rate of regurgitant flow must be measured as cubic centimeters per systolic second. The rate of regurgitant flow can be determined only if the amount of blood regurgitating per minute and the time duration of regurgitation per minute, the duration of ventricular systole, are known. This may be expressed as follows:

$$3.\quad MRF = \frac{Fr}{SEP}$$

where MRF = rate of mitral regurgitant flow (c.c. per systolic second)
Fr = amount of mitral regurgitant blood flow (c.c. per minute)
SEP = systolic ejection period (systolic seconds per minute).

The systolic ejection period per beat can be approximated by analysis of the brachial arterial tracing by methods described previously[6] and as discussed in detail later. This period, when multiplied by the pulse rate, gives the systolic ejection period per minute.

If one knows the total ventricular inflow or output and the effective or aortic output, then the regurgitant flow should be the difference between the two. This principle was used by Keys and Friedell.[5] They determined the cardiac output by roentgenkymography and the Fick method and considered the difference between the two as the regurgitant volume. This may be expressed as follows:

$$4.\quad Fr = Fm - CO$$

where Fr = regurgitant flow (c.c. per minute)
Fm = total left ventricular flow (c.c. per minute)
CO = effective or aortic cardiac output (c.c. per minute).

If equation 4 is now substituted in equation 3, then

$$5.\quad MRF = \frac{Fm - CO}{SEP}$$

and if equation 5 is substituted in equation 2, then one derives

$$6.\quad MRA = \frac{Fm - CO}{C \times SEP \times 44.5 \sqrt{LV_{sm} - LA_m}}$$

The only value that cannot be readily measured in this formula is Fm.

Total Amount of Left Ventricular Flow (Fm).—The total left ventricular outflow cannot be measured directly by present methods. We have attempted to determine total flow by the orifice flow meter principle.[13] In the steady state, ventricular inflow must equal outflow. The amount of ventricular inflow depends on the area of the valve orifice during diastole, the pressure gradient exerted upon it during diastole, and the time duration of that part of the cardiac cycle when inflow occurs, namely the diastolic filling period. This may be demonstrated by solving the standard forward valve area equation[6] for total left ventricular inflow (Fm) as follows:

$$7.\quad MVA = \frac{\frac{Fm}{DFP}}{C \times 44.5 \sqrt{LA_m - LV_{md}}}$$

$$8.\quad Fm = MVA \times DFP \times C \times 44.5 \sqrt{LA_m - LV_{md}}$$

where Fm = total left ventricular inflow (liters per minute)
MVA = forward mitral valve area (cm.^{2})
DFP = diastolic filling period (diastolic seconds per minute)
C = empirical constant
44.5 = $\sqrt{2g} = \sqrt{1960}$
LA_m = left atrial mean pressure (mm. Hg)
LV_{md} = left ventricular mean diastolic pressure (mm. Hg).

In this manner, the mitral valve is used as an orifice flow meter[13] to determine total flow (Fm). If equation 8 for Fm is substituted in equations 4 and 6, one derives the final expressions for regurgitant flow and valvular areas:

$$9.\quad Fr = MVA \times DFP \times C \times 44.5 \sqrt{LA_m - LV_{md}} - CO$$

$$10.\quad MRA = \frac{MVA \times DFP \times C \times 44.5 \sqrt{LA_m - LV_{md}} - CO}{SEP \times C \times 44.5 \sqrt{LV_{sm} - LA_m}}$$

The area formula is now expressed almost entirely in terms of blood pressures and flows, the only anatomic measurement being the forward mitral valve area. Pressures and flows may be measured directly or approximated indirectly. The forward valve area must be measured directly. If no valve area is available, then the equation may be considered to express a ratio between the forward and the regurgitant areas. All values entering the equation are measured in the centimeter-gram system. Pressures are recorded as millimeters of mercury but are converted to centimeters of water by the number 1.36. Because the square root of pressure is used in the equation, the square root of the conversion factor, 1.17, is incorporated in the C factor.

METHODS

On the day of study, the patients fasted or else received a light breakfast of orange juice, toast, jam, and black coffee. Cardiac catheterization was performed in the usual fashion. Phasic and mean pulmonary "capillary" pressures[14] were recorded at rest (after five minutes or more, during which time pulse and respiration had become stable) and in some of the studies again during exercise (at the second minute of a three-minute period of exercise as described later). Sufficient time was allowed between exercise periods to allow pulse and respiration to return to normal, usually ten minutes or more.

The catheter was then withdrawn to a point just distal to the bifurcation of the pulmonary artery. A No. 20 or 21 short-bevel needle was inserted into the brachial artery, the lumen of which was kept patent by a slow intra-arterial saline solution infusion. After pulse and respiration had returned to the initial resting level, a resting effective or aortic cardiac output was measured by the direct Fick method. Expired air was collected for three minutes in a Douglas bag, and blood samples were withdrawn simultaneously from the brachial artery and pulmonary artery midway during the gas collection. Immediately thereafter, pressures in the pulmonary and brachial arteries were recorded. In those patients who were exercised, pressures were taken after two minutes of exercise. Expired air was collected between 2.5 and 3.0 minutes. Midway during the collection of the expired air, blood samples were withdrawn from the pulmonary and systemic arteries simultaneously. The volume of expired air was measured in a Tissot spirometer, and the concentration of oxygen alone was measured by a Pauling oxygen analyzer. From previous studies[15] of the Haldane analysis of expired air, mean correction factors of 1.007 and 1.01 were derived for converting expired volume to inspired volume under resting conditions and during exercise, respectively. Blood samples were analyzed for oxygen content, capacity, and saturation by the method of Van Slyke and Neill,[16] and the arteriovenous oxygen difference was calculated.

Pressures were measured with electromanometers*[17] which recorded on a multi-channel, direct-writing oscillograph. The recording was calibrated with a mercury manometer after each pressure tracing. The zero point for all pressures was 10 cm. anterior to the back with the patient recumbent. A saline manometer was used for checking mean pressures but not for analytical purposes. Mean pressures were obtained by electrical integration of the oscillographic tracings. Brachial arterial systolic mean pressures were obtained by planimetric integration.

Exercise was performed with the patient recumbent, pedalling a bicycle at the rate of 56 r.p.m., timed with a metronome.

Substitution of Data in the Mitral Valve Regurgitant Formulas

The formula for calculation of the regurgitant blood flow (Fr) in which values are substituted in equation 9 is as follows:

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$$11.\quad Fr = MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5} - CO$$

where MVA = forward mitral valve area (cm.^{2})
DFP = diastolic filling period (seconds per minute)
$31 = C \sqrt{2g} = 0.7 \sqrt{1960}$
"PC" = pulmonary "capillary" pressure (mm. Hg)
5 = assumed left ventricular diastolic pressure (mm. Hg)
CO = aortic cardiac output (liters per minute).

The formula for the calculation of the cross-sectional area of the regurgitant mitral orifice (MRA) in which values are substituted in equation 10 was as follows:

$$12.\quad MRA = \frac{MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5} - CO}{SEP \times 36 \sqrt{BA_{sm} - \text{"PC"}}}$$

where SEP = systolic ejection period (systolic seconds per minute)
$36 = C \sqrt{2g} = 0.8 \sqrt{1960}$
BA_{sm} = brachial arterial systolic mean pressure (mm. Hg).

The factors entering these equations are as follows:

A. Amount of Mitral Regurgitant Flow (Fr).—The amount of regurgitant flow is equal to the total left ventricular output (Fm) minus the effective or aortic output (CO). The total left ventricular output which equals total diastolic inflow may be calculated as described in an earlier section.

The factors from which the amount of regurgitant flow may be derived are discussed in order.

I. Total left ventricular inflow: 1. Forward mitral valve area. The forward mitral valve area is defined as the narrowest area of the valvular orifice during ventricular diastole. In the nonstenotic valve, this will be the area at the level of the valve ring. In the stenotic valve, this will be the area formed by the fused anterior and posterior valve cusps which is displaced lower into the left ventricle. This area is readily measured at autopsy or by intracardiac digital palpation at the time of mitral valvuloplasty. Errors in estimation of area by digital palpation have not been great; autopsy measurement and repeated palpation of the mitral orifice have checked within 0.1 to 0.2 cm.^{2} in seven patients where both measurements were available. The digital method is reliable up to an area equal to the size of the surgeon's index finger, which in our particular case was 2.5 cm.^{2}*

2. Diastolic filling period. Ventricular inflow occurs only during diastole, which occupies a variable portion of each cardiac cycle, depending on pulse rate and the duration of systole.[18] This period may be approximated on the brachial arterial tracing as described elsewhere.[6] This is then multiplied by the pulse rate per minute to give the diastolic filling period in seconds per minute.

3. Pressure gradient across the mitral valve during diastole ($P_1 - P_2$, or "PC" − 5). P_1 is left atrial mean and P_2 left ventricular mean diastolic pressure

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Previous studies[19] have indicated that pulmonary "capillary" pressure may be used as a reliable measure of left atrial pressure and therefore as P_1 in this equation. P_2 cannot be measured by right heart catheterization techniques. As in the case of pure mitral stenosis, a value of 5 mm. Hg was assumed for left ventricular mean diastolic pressure.

The assumption of a left ventricular diastolic pressure of 5 mm. Hg in the presence of mitral insufficiency, wherein the ventricular work load is often greater than normal, should be discussed. Up to a point, the ventricles tolerate large flows without a change in diastolic pressure. Thus, in six patients with patent ductus arteriosus,[20] the pulmonary "capillary" pressure was within normal limits despite left ventricular blood flows ranging from 3.3 to 18.3 L. per minute per square meter. Zimmerman[21] reported normal left ventricular diastolic pressures in three patients with aortic insufficiency. In six patients with atrial septal defect[20] with right ventricular blood flows ranging from 5.5 to 19.0 L. per minute per square meter, the right ventricular diastolic pressure was not elevated unless mitral stenosis or an atrophic left ventricle was also present. Patients with mitral regurgitation also apparently can deliver normal or increased left ventricular blood flows without marked elevations of diastolic filling pressure. This could be deduced from observations of the level of pulmonary "capillary" end diastolic pressure[4] which is, in turn, dependent on the level of the left ventricular diastolic pressure, the degree of mitral stenosis, and the heart rate.[20] In two patients (E. L. and M. S.) with mitral insufficiency who did not have severe mitral stenosis or severe tachycardia, the pulmonary "capillary" diastolic pressures were 5 and 6 mm. Hg, respectively, despite the fact that the total left ventricular stroke volumes were increased in both patients.[4]

Thus the presence of increased left ventricular blood flow does not necessarily entail an elevation of left ventricular diastolic pressure unless these flows are truly excessive. Such has not been observed in our patients with mitral insufficiency.[4] The main factor which can introduce an elevated left ventricular diastolic pressure and which is not always easily recognizable is active rheumatic carditis. It is believed, but not possible to prove, that none of the patients here reported had this complication.

Because no direct measurements have been made, it was decided, as in the case of mitral stenosis, to assume 5 mm. Hg as the left ventricular diastolic pressure for purposes of our calculations. The purpose of this report is to present methods for obtaining a semiquantitative picture of mitral insufficiency. The assumption of 5 mm. Hg as the left ventricular diastolic pressure will not prevent such a demonstration because, if anything, the magnitude of blood flow and the size of regurgitant areas will be overestimated rather than underestimated by this assumption. The magnitude of the possible errors in calculation of flow and area, when 5 mm. Hg is used, varied from -20 per cent to -60 per cent, depending on the height of the pulmonary "capillary" pressure and the value assumed for left ventricular diastolic pressure. As in mitral stenosis,[6] the larger the valvular gradient, the less the error introduced by the assumed diastolic pressure.

4. Empirical constant. The empirical constant corrects for (a) hydraulic losses through an orifice, (b) errors in indirectly calculating diastolic filling period

(c) the conversion from millimeters of mercury to centimeters of water. As described elsewhere,[6] this value was found to be 0.7.

Total left ventricular inflow (Fm) is then computed from pressure and area measurements, the orifice flow meter principle being applied to the mitral valve.

II. Effective or aortic output (CO): The effective or aortic blood flow is measured by the direct Fick method. If the effective output (II) is subtracted from the total ventricular output (I), the resulting value is the amount of regurgitant flow per minute (Fr).

B. Mitral Valve Regurgitant Area (MRA).—The mitral regurgitant area may be computed from the standard orifice equation. The factors entering this equation are discussed here.

I. Rate of mitral regurgitant flow: Mitral regurgitant flow is obtained by dividing the amount of regurgitant flow per minute by the systolic ejection period per minute.

1. Amount of regurgitant flow. The method for deriving this value has been discussed.

2. Systolic ejection period (SEP). The amount of regurgitant blood flow is reckoned in liters per minute, but blood is regurgitated only during that portion of the cardiac cycle occupied by ventricular systole. The duration in seconds of the systolic period gives the number of seconds per minute during which blood is regurgitated. This period is called the systolic ejection period.

Strictly speaking, regurgitation begins a few hundredths of a second after ventricular systolic pressure exceeds left atrial pressure and ends a few hundredths of a second after atrial pressure exceeds ventricular pressure. The time lags are due to the fact that a certain amount of pressure energy must be expended in reversing valvular flow. Wiggers and Feil first demonstrated this fact in the dog with experimental mitral insufficiency by means of auricular cardiometers.[22] Regurgitation apparently did not occur during the first 0.04 second of systole and actually continued into the periods of diastole. In mitral insufficiency in man, however, where valve flow velocities seldom exceed 300 c.c. per second, only 5 to 10 mm. Hg of pressure are required to reverse the direction of blood flow. Pressure rises and falls so rapidly during the isometric periods[18] that delays in the beginning and cessation of regurgitation are probably only 0.01 to 0.02 second, respectively.

No measurements of the period of systolic regurgitation have been made directly on left ventricular tracings because left ventricular catheterizations have not been performed. They have been made instead on brachial arterial tracings. By this method the measured duration of systole does not include the periods of isometric contraction and relaxation, which are included in total diastole.[18] Hence, our estimations of systolic ejection are slightly shorter than actually obtain. In the presence of associated mitral stenosis or if regurgitation is severe, atrial pressures are much higher than normal. As a result, regurgitation does not begin probably until midway through isometric contraction, when ventricular pressure finally exceeds atrial pressure by 5 to 10 mm. Hg, and ceases midway through isometric relaxation, when atrial pressure exceeds ventricular pressure by 5 to 10 mm. Hg and diastolic inflow begins. Because of (a) the

increased left atrial pressure and (b) the slight time lags in the occurrence of regurgitation, our value probably does not underestimate left ventricular regurgitant ejection time by more than 0.05 second.

Systolic ejection period per beat, when multiplied by the heart rate, gives the systolic ejection period per minute.

II. Pressure gradient across the mitral valve during regurgitation ($P_1 - P_2$, *or* $BA_{sm} -$ *"PC"*): P_1 is left ventricular mean systolic ejection pressure. P_2 is left atrial mean pressure. Studies of congenital heart disease[23] have demonstrated a near identity of mean systolic pressure as recorded in the right and/or left ventricle, aorta, and brachial artery. Brachial arterial pressure is similar to the others because the recording needle is end-on to the stream wherein the velocity component was converted back into pressure.[6] From these observations, it was inferred that the brachial arterial mean systolic pressure, as recorded through a needle, could be used as a reliable index of aortic mean systolic pressure and in the absence of aortic stenosis could be considered as within a few millimeters of mercury of intraventricular mean systolic ejection pressure because of the large orifice at the aortic valve. Brachial arterial mean systolic pressure, therefore, is used as P_1 in the formula. As discussed elsewhere,[19] pulmonary "capillary" pressure is a reliable index of left atrial pressure and as such was used as P_2 in the mitral regurgitant pressure gradient. Because the gradient was so large, no effort was made to determine the exact pulmonary "capillary" pressure during regurgitation, which actually was no more than 2 to 5 mm. higher than the mean pressure. The fact that the square root of the pressure gradient was used in the formula further minimized any errors introduced in the indirect measurement of pressures here.

III. Empirical constant (C): This factor should correct for (a) hydraulic losses through the regurgitant orifice, (b) the conversion of millimeters of mercury to centimeters of water ($\sqrt{1.36} = 1.17$), and (c) errors introduced by the method of measurement of the systolic ejection period. "C" cannot be determined empirically because it is not possible to measure regurgitant valve areas anatomically for comparison with calculated areas. Certain theoretical considerations may be made, however, regarding the selection of this constant. The discharge coefficient of the orifice would be in the neighborhood of 0.6 to 0.7 for a water-iron pipe system because the orifice partly protrudes into the left ventricle and is exposed to a high pressure head.[13] This must be corrected upward by 1.17 for the mercury conversion factor and by 1.16, which theoretically corrects for the underestimation of the period of ventricular systole when measured on a brachial arterial pulse tracing. Without being able to compare anatomic and calculated orifices, no better approximation can be made. It is appreciated that blood viscosity and tissue surface smoothness will introduce some effects, immeasurable by our techniques, which are different from water flowing through iron pipes. The empirical constant as derived partly from theoretical considerations was 0.8.

RESULTS

Studies have been made on ten patients. In patient L. L., the forward area of the mitral valve was obtained at autopsy. In five patients, the forward area

of the mitral valve was obtained at the time of mitral valvuloplasty by intracardiac digital palpation before and after widening of the valve orifice. Patient M. S. had had a mitral systolic murmur since birth associated with left ventricular hypertrophy which was presumed due to congenital mitral insufficiency. In the absence of clinical signs and symptoms of mitral stenosis, a normal valve area of 4 cm.^{2} for her age was assumed for purposes of calculation. In three patients (F. K., L. C., and E. S.) with mitral insufficiency and stenosis in whom no autopsy or operative estimates of valve area were available, forward valve areas of 2 cm.^{2} were utilized in the formula for purposes of demonstrating (a) the reproducibility of calculations for valve area and (b) the interrelationship of forward and regurgitant valve areas. Although any other value could have been chosen, 2 cm.^{2} was equal to the average area of the patients with known valve areas. In addition, the effective valve areas alone in these three patients averaged 1.1 cm.^{2} The calculation of effective area is based on the effective or aortic blood flow as measured by the direct Fick method.[6] Because total blood flow is much larger in the presence of regurgitation, the true forward valve area must have been larger than 1.1 cm.^{2}

A typical calculation is as follows:

Patient E. D.

Forward mitral valve area (MVA) = 1.5 cm.^{2}
Effective cardiac output (CO) = 2.8 liters per minute.
Diastolic filling period per beat = 0.35 second per beat
Systolic ejection period per beat = 0.26 second per beat
Pulse rate = 98
Diastolic filling period per minute (DFP) = 34 seconds per minute
Systolic ejection period per minute (SEP) = 26 seconds per minute
Pulmonary "capillary" pressure ("PC") = 21 mm. Hg
Left ventricular diastolic pressure (assumed) = 5 mm. Hg
Brachial arterial systolic mean pressure (BA_{sm}) = 117 mm. Hg

11. *Amount of Regurgitant Flow*

$$Fr = MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5} - CO$$

$$Fr = 1.5 \times 34 \times 31 \sqrt{21 - 5} - 2.8$$

$$Fr = 6.4 - 2.8 = 3.6 \text{ liters per minute}$$

12. *Mitral Regurgitant Area*

$$MRA = \frac{MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5} - CO}{SEP \times 36 \sqrt{BA_{sm} - \text{"PC"}}}$$

$$MRA = \frac{3.6}{26 \times 36 \sqrt{117 - 21}}$$

$$MRA = 0.4 \text{ cm.}^2$$

Thus knowing the forward mitral valve area, it was possible to estimate the mitral regurgitant area. Values ranged from 0.3 to 0.8 cm.^{2} in the five patients with known forward valve areas. It is to be noted that in only one out of thirteen calculations was the regurgitant area 50 per cent or more of the forward area of the mitral valve. The patient who was the exception had the smallest mitral

valve and was severely incapacitated. Because there was no way of comparing autopsy and calculated areas, the only check on the method was repeated calculation of regurgitant area in the same patient, and at the beginning of the study it was not known whether the regurgitant defect was a fixed orifice. Six patients were studied a total of seven times at rest, during exercise, and on recovery from exercise. In six instances, the resulting regurgitant areas checked within 0.1 cm.^{2} and within 0.2 cm.^{2} in the seventh.

DISCUSSION

Calculation of the area of the regurgitant valve orifice has three major aims. The first is to describe from physiologic data some of the anatomic features of the mitral regurgitant orifice. The fact that the area was calculated to be the same under different circulatory conditions would suggest that the orifice formed by defective valve closure apparently is fixed or at least not widely varying from moment to moment.

The regurgitant areas were quite small, being less than 1 cm.^{2} as calculated. The lack of an accurate empirical constant in the area formula partly limits (1) true estimation of regurgitant valve area and (2) comparison of regurgitant and forward valve areas because the former is only a gross approximation of the true area, while the latter is actually measured anatomically. Therefore, only rough conclusions may be drawn about the size of the regurgitant orifice or about the relationship between the two mitral orifices. Nevertheless, even if very low orifice coefficients are assumed in the formula, the calculated area will be quite small and definitely no more than 0.1 to 0.2 cm. larger than the values reported herein and therefore less than the forward valve area.

This finding would seem to be indicated on theoretical grounds also. The atrioventricular pressure gradient during diastole is much less than the ventriculoatrial gradient during systole. Although more time is ordinarily available for diastolic inflow than for systolic discharge, it is apparent that unless the forward orifice is larger than the regurgitant orifice, less blood will flow into the ventricle during diastole than could be theoretically regurgitated during systole because of the existing differences in pressure heads. One must conclude on both experimental and theoretical evidence that the mitral valve decreases in area with systole. Pathologic examination often reveals poor cusp action and frequently a fish-mouth orifice. The apparent decrease in valve area, even with marked stenosis (Patient E. L.), presupposes a mechanism of valve orifice closure. In the absence of mobile cusps, two possible mechanisms may come into play: (1) The walls of the valve may be forcibly squeezed *toward* one another by ventricular systolic pressure, or (2) the valve orifice is partly occluded by the ventricular wall itself, papillary muscles, or thickened chordae tendineae. That valve action is not necessary if the orifice is oriented posteriorly toward the ventricular wall is suggested by observations of Harken[10] during valvuloplasty and of Denton and associates[24] with artificial mitral valves.

The regurgitant areas were all small in relation to the normal aortic orifice of 4 to 6 cm.^{2} This would have to be the case in order for life to continue,

because the regurgitant pressure gradient is so much larger than that across the aortic valve orifice where actually there is very little orifice action.

The relatively small size of the regurgitant orifice becomes of practical importance in the planning of surgery for relief of mitral regurgitation. The critical difference between a large or small amount of regurgitation is only a matter of 0.5 cm.^{2} in area. Accurate operative appraisal of the exact site of the leak and individual planning of the appropriate procedure at the time of intracardiac palpation are of utmost importance. If properly located, very little anatomic obstruction is needed to close the small orifice. Either better apposition of valve leaflets through mobilization[10] or a small, properly placed baffle during systole may eliminate or at least curtail regurgitation.

In this small group of patients none of the measured stenotic areas was less than 1.1 cm.^{2} The calculated effective area, which is based on effective and not on true or total blood flow[6] and indicates a smaller valve area than really exists, was found to average 1.1 cm.^{2} in the three patients without a measured valve area. Thus, none of our patients had mitral stenosis less than 1.0 cm.,^{2} while 80 per cent of our patients with pure mitral stenosis and similar degrees of disability had valve areas of 1 cm.^{2} or less.[25] This and the frequency of pure tight mitral stenosis[3] would suggest that significant regurgitation is more often seen when the stenosis is mild than when it is severe, probably because both severe stenosis and severe regurgitation are incompatible with life.[4] It may be conjectured that unless regurgitation becomes less as the stenosis progresses, death supervenes.

The second purpose in calculating regurgitant areas is to aid in describing and interpreting the circulatory dynamics of mitral regurgitation,[4] which depend so much on the size of the regurgitant defect. The lack of a known empirical constant did not affect the use of calculated values for regurgitant area as long as they were considered in relation to one another, as was done in this study. Much valuable information on the interplay of factors can be obtained even without accurate area measurements.

The third purpose of the method is to attempt to evaluate mitral regurgitation before and after valvular surgery. Regurgitation can be detected qualitatively from the height of the V wave in the pulmonary "capillary" pressure pulse.[4] It is not possible to evaluate regurgitation quantitatively without knowing the forward valve area. It is possible, however, to calculate the ratio of regurgitant to forward area and obtain some idea of the size of the regurgitant orifice at different degrees of stenosis. There appears to be a rough inverse relation of the aortic output to the forward valve area,[4] and an approximation of the range of the stenotic area can be made from the value for aortic cardiac output. With an idea of the magnitude of the stenotic area, decision can be made as to the severity of the calculated regurgitant defect. Second, in converse fashion, one can judge the severity of the stenosis by assuming varying degrees of regurgitation and calculating the stenotic area. Regurgitant flow seldom was observed to be more than twice the forward flow.[4] For example, if the forward valve area were calculated from the stenotic mitral valve area formula to be 1.5 cm.^{2} or

TABLE I. DATA RELATIVE TO CALCULATION OF MITRAL REGURGITANT AREA

PATIENT	STATE*	DIASTOLIC FILLING PERIOD (SECONDS PER BEAT)	SYSTOLIC EJECTION PERIOD (SECONDS PER BEAT)	PULSE RATE	DIASTOLIC FILLING PERIOD (SECONDS PER MINUTE)	SYSTOLIC EJECTION PERIOD (SECONDS PER MINUTE)	LEFT VENTRICULAR OUTPUT (LITERS PER MINUTE)			MITRAL VALVE FLOW (C.C. PER SECOND)			MEAN PRESSURES (MM. Hg)		MITRAL VALVE AREA (CM.²)†		
							AORTIC	TOTAL	REGURGITANT	FORWARD		REGURGITANT	PULMONARY "CAPILLARY"	BRACHIAL ARTERIAL SYSTOLIC	FORWARD		REGURGITANT
										EFFECTIVE	TOTAL				EFFECTIVE	TRUE	
M. S.	R	0.27	0.28	109	29.5	30.5	5.9	9.7	3.0	200	329	125	12	83	2.4	4.0	0.4
L. L.	R	0.60	0.27	69	41	19	4.5	10.1	5.6	110	247	295	12	110	1.3	3.0	0.8
	E	0.32	0.23	110	35	25	5.0	13.0	8.0	143	371	320	21	110	1.2		0.9
E. D.‡	R	0.35	0.26	98	34	26	2.8	6.4	3.6	82	185	138	21	117	0.7	1.5	0.4
E. L.	R	0.46	0.20	91	42	18	2.0	6.3	4.3	48	150	239	24	108	0.4	1.1	0.7
E. L.‡	R	0.48	0.22	86	41	19	2.6	6.4	3.8	63	156	200	10	90	0.9	2.3	0.6
A. D.	R	0.25	0.21	130	32.5	27.5	3.1	7.4	4.3	95	228	156	37	118	0.5	1.3	0.5
	E	0.24	0.19	140	34	26	3.9	8.0	4.1	115	235	158	39	129	0.6		0.5
A. D‡	R	0.36	0.29	92	33	27	3.6	8.9	5.3	109	270	196	26	94	0.8	1.9	0.7
M. D.	R	0.38	0.25	96	36.5	23.5	5.7	8.5	2.8	156	233	119	27	135	1.1	1.6	0.3
	E	0.32	0.23	110	35	25	6.1	9.0	2.9	174	257	116	32	154	1.1		0.3
	R′	0.38	0.25	94	36	24	5.5	8.4	2.9	153	233	121	27	124	1.1		0.3
M. D.‡	R	0.29	0.21	120	35	25	4.7	7.8	3.1	134	223	124	23	120	1.0	1.7	0.4
	E	0.22	0.18	150	33	27	5.5	9.1	3.6	167	276	133	32	125	1.0		0.4
	R′	0.33	0.24	105	35	25	4.4	7.8	3.4	126	223	136	23	132	1.0		0.4
D. N.	R	0.76	0.34	55	42	18	3.8	7.5	3.7	91	179	206	18	110	0.8	1.6	0.6
F. K.	R	0.23	0.27	120	28	32	5.1	7.1	2.0	182	253	63	22	89	1.4	2§	0.2
	E	0.16	0.24	150	24	36	5.8	9.7	3.9	242	404	108	48	112	1.2		0.4
	R′	0.30	0.26	107	32	28	6.2	8.4	2.2	194	262	79	23	90	1.5		0.3
E. S.	R	0.44	0.29	82	36	24	4.4	9.7	5.3	122	270	221	24	123	0.9	2§	0.7
	E	0.32	0.28	100	32	28	5.3	10.9	5.6	166	341	200	35	129	1.0		0.6
	R′	0.48	0.30	77	37	23	4.6	9.2	4.6	124	249	200	21	124	1.0		0.6
L. C.	R	0.51	0.32	72	37	23	3.5	9.2	5.7	95	249	248	21	95	0.8	2§	0.8
	E	0.32	0.28	100	32	28	4.4	11.4	7.0	138	356	250	38	120	0.8		0.8
	R′	0.50	0.31	74	37	23	3.5	9.7	6.2	95	262	270	23	97	0.7		0.9

*R = rest
E = exercise
R′ = recovery from exercise

†Effective mitral valve area is that area calculated as if mitral insufficiency were not present. True mitral valve area is the area as measured at necropsy by the surgeon at operation.

‡Study done two to four weeks after mitral valvuloplasty.

§Arbitrary value assigned for purposes of making repeated calculations of regurgitant area.

less when the total flow equals three times the aortic output, then stenosis would be an important part of the valvular pathology.

Postoperative evaluation is readily carried out if the pre- and postvalvuloplasty valve areas are known from digital palpation. Such was the case in patients E. L., A. D., and M. D. Each had regurgitation before operation. In none of them did the calculated regurgitant area change appreciably over the preoperative value (Table I), although the stenotic area was widened in two.

In similar fashion, these formulas may be used to evaluate the effects of surgery aimed primarily at the correction of mitral regurgitation. As previously stated, all that is required, in addition to pre- and postoperative cardiac catheterization, is a digital estimate of the forward area of the mitral valve. Then the regurgitant area before and after operation may be calculated. Gross reductions in regurgitation should be readily detected by this technique.

The formula may be used in another way; the *ratio* of regurgitant to forward area may be calculated rather than deriving actual values for area. If the ratio decreases following operation, it is fair to conclude that at least some improvement has been achieved. Either the stenotic orifice has been widened or the regurgitant area has been decreased. It must be emphasized at this point that the answers derived from this formula are meant to be *indices* of the true values. While in the three cases presented areas checked well, this may not always be so. Therefore caution must be used in attaching final significance to the results of this calculation until more experience with the methods is available. Until then, it is advisable to pool all available information, as the height of the V wave in the pulmonary "capillary" pulse tracing, fluoroscopy, and changes in murmurs on auscultation, in deciding what happened to the regurgitant lesion postoperatively.

The formulas, although theoretically correct, fall heir to many practical weaknesses. The values entering the formulas are, in the main, indirect measures of inaccessible or unknown values. Despite this, it has been possible to obtain reproducible answers on repeated calculations suggesting (1) that the regurgitant orifice is fixed and (2) that compensation of errors occurs within the equation. The major variable is the assumed left ventricular diastolic pressure. Except for the variations in this pressure, calculations can be readily compared from one patient to another or in one patient at different times of study. Great care must be taken to exclude the presence of rheumatic myocarditis. In the absence of myocarditis, as pointed out earlier, the heart probably handles chronic but not excessive elevations of blood flow at normal filling pressures.

In the given patient, when feasible, it is always best to make observations during different dynamic states so as to derive check answers for regurgitant area and also to observe the effects of exercise on regurgitation. Because of the method and techniques used, the answers so derived are only meant to be semiquantitative. The areas are only an index of what may be the actual anatomic valvular defect, although in relation to each other values obtained from this hydraulic approach have relative but not absolute validity. Their greatest use will be in descriptive analysis, as in demonstrating the circulatory dynamics of valvular regurgitation where precision is not the uppermost consideration.

§Arbitrary value assigned for purposes of making repeated calculations of regurgi-

These formulas may be adapted for study of the regurgitant tricuspid valve. The major problems here are (1) the almost immeasurable atrioventricular pressure gradient during diastole and (2) the lack of empirical orifice constants for either the forward or regurgitant valve orifices.

CONCLUSIONS

1. An indirect approach to the quantitative aspects of mitral valvular regurgitation has been made by means of hydraulic principles with the realization that values so derived are indices of the true values.

2. The two principles employed were (a) total ventricular flow equals regurgitant flow plus aortic flow and (b) the standard hydraulic orifice formula, where

$$\text{orifice area equals } \frac{\text{rate of flow}}{\text{constant} \times \sqrt{2 \times \text{gravity acceleration} \times \text{pressure gradient}}}.$$

3. The final formulas were:

a. $$Fr = MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5} - CO$$

b. $$MRA = \frac{MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5} - CO}{SEP \times 36 \sqrt{BA_{sm} - \text{"PC"}}}$$

where Fr = regurgitant blood flow (liters per minute)
MVA = forward mitral valve area (cm.²)
DFP = diastolic filling period (seconds per minute)
31 = empirical constant
"PC" = pulmonary "capillary" mean pressure (mm. Hg)
5 = assumed left ventricular mean diastolic pressure (mm. Hg)
CO = aortic output (liters per minute)
MRA = mitral regurgitant area (cm.²)
SEP = systolic ejection period (seconds per minute)
36 = empirical constant
BA_{sm} = brachial arterial systolic mean pressure (mm. Hg)

4. In addition to pressure and flow data, it was necessary to know the forward area of the mitral valve in order to make these calculations. This was measured either at autopsy or by digital palpation at the time of surgery.

5. Areas calculated in the same individual under different circulatory states checked within 0.1 cm.² in six instances and within 0.2 cm.² in the seventh.

6. Regurgitant areas ranging from 0.3 to 0.9 cm.² were calculated; they were always less than the mitral valve forward area and usually about one-fourth to one-tenth the size of the aortic valve.

7. The results of the calculations may be used in (a) eliciting some of the functional and anatomic characteristics of the regurgitant orifice, (b) describing the circulatory dynamics of mitral regurgitation, and (c) evaluating regurgitation before and after surgery on the mitral valve.

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REFERENCES

1. Cournand, A., and Ranges, H. A.: Catheterization of Right Auricle in Man, Proc. Soc. Exper. Biol. & Med. **46**:462, 1941.
2. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of Right Heart Pressures in Normal Subjects and in Patients With Chronic Pulmonary Disease and Various Types of Cardio-circulatory Disease, J. Clin. Investigation **25** :639,1946.
3. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the Circulatory Dynamics in Mitral Stenosis. II. Altered Dynamics at Rest, AM. HEART J. **41**:30, 1951.
4. Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L.: Studies of the Circulatory Dynamics at Rest in Mitral Valvular Regurgitation With and Without Stenosis, AM. HEART J. To be published.
5. Keys, A., and Friedell, H. L.: Quantitative Measurement of Valvular Efficiency of the Human Heart, Proc. Soc. Exper. Biol. & Med. **40**:556, 1939.
6. Gorlin, R., and Gorlin, S. G.: Hydraulic Formula for Calculation of the Area of the Stenotic Mitral Valve, Other Cardiac Valves, and Central Circulatory Shunts, AM. HEART J. **41**:1, 1951.
7. Smith, H. C., Essex, H. E., and Baldes, E. J.: A Study of the Movement of Heart Valves and of Heart Sounds, Ann. Int. Med. **33**:1357, 1950.
8. James F. Dickson: Unpublished observations.
9. Harken, D. E., Ellis, L. B., Ware, P. F., and Norman, L. R.: The Surgical Treatment of Mitral Stenosis. I. Valvuloplasty, New England J. Med. **239**:801, 1948.
10. Harken, D. E.: Personal communication.
11. Landowne, M., and Katz, L. N.: Heart: Work and Failure in Medical Physics, Chicago, 1944, Year Book Publishers, Inc.
12. Gorlin, S. G.: Personal communication.
13. Daugherty, R. L.: Hydraulics, New York, 1937, McGraw-Hill Book Company, Inc.
14. Hellems, H. K., Haynes, F. W., and Dexter, L.: Pulmonary "Capillary" Pressure in Man, J. Applied Physiol. **2**:24, 1949.
15. Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R., and Sawyer, C. G.: Effect of Exercise on the Circulatory Dynamics of Normal Individuals, J. Applied Physiol. **3**:439, 1951.
16. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. II, Methods, Baltimore, 1932, Williams & Wilkins Company.
17. Rappaport, M., and Sarnoff, S. J.: An Electronic Multi-Range, Multi-Channel, Direct-Writing Pressure Recorder, Federation Proc. **8**:130, 1949.
18. Wiggers, C. J.: Modern Aspects of the Circulation in Health and Disease, Philadelphia, 1923, Lea & Febiger.
19. Dow, J. W., and Gorlin, R.: Pulmonary "Capillary" Pressure as an Index of Left Atrial Mean Pressure in Dogs, Federation Proc. **9**:33, 1950.
20. Unpublished observations.
21. Zimmerman, H. A.: Left Ventricular Pressures in Patients With Aortic Insufficiency Studied by Intracardiac Catheterization, J. Clin. Investigation **29**:1601, 1950.
22. Wiggers, C. J., and Feil, H.: The Cardiodynamics of Mitral Insufficiency, Heart **9**:149, 1922.
23. Dexter, L.: Cardiac Catheterization in the Diagnosis of Congenital Heart Disease, Bull. New York Acad. Med. **26**:93, 1950.
24. Denton, G. R., Mastriani, B., Brown, C., Jr., and Wiggers, H. C.: Physiological Effects of Plastic Prosthesis for Mitral Valves in Dogs, Federation Proc. **9**:31, 1950.
25. Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: Clinical and Physiological Correlations in Patients With Mitral Stenosis, AM. HEART J. **43**:2, 1952.

ALTERATIONS OF THE RAPID FILLING PHASE IN CONGESTIVE HEART FAILURE

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THE majority of physiological measurements of mechanical efficiency of the human heart have heretofore been concerned primarily with the process of cardiac emptying, as measured by stroke volume and cardiac output. Recently, Harrison and associates[1] and also Howarth, McMichael, and Sharpey-Schafer[2] have emphasized the importance of the relationship of cardiac output to venous inflow load, a conception based in part upon the original observations of Starling[3] with the heart-lung preparation. The importance of alterations in the filling phase of the cardiac cycle, however, has until recently received little attention in human beings.

The development of the electrokymogram has made available a convenient method for recording directly the duration and contour of the rapid filling phase in human hearts. Such data concerning the rapid filling phase have been obtained previously in the experimental animal only by recording the volumetric changes obtained by placing the heart in a cardiometer. Similar observations have not been systematically recorded in patients suffering from congestive heart failure. It is the purpose of the present communication to report observations concerning the duration of the rapid filling phase, as well as of other phases of the cardiac cycle, in patients with chronic myocardial insufficiency and to compare these results with a series of similar observations made in normal healthy human subjects.

METHOD OF STUDY

A series of thirty-one normal subjects was studied; a string galvanometer and the electrokymographic apparatus previously described by Henny and coworkers[4] were utilized. These observations were made mainly with the subject in the sitting position, although a few were recorded in the standing position. Records were made after the subject sat quietly at rest for a period of five to ten minutes, and all normal subjects were free of any detectable evidence of cardiac disease on physical examination. A group of nineteen patients suffering from congestive heart failure was studied in a similar manner. The clinical and

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laboratory data for this group of nineteen patients are summarized in Table I. It will be noted that these patients had variable degrees of dyspnea and ankle edema. None of the patients was receiving digitalis at the time of the original electrokymographic tracing. Patients with disease of the mitral and aortic valves were excluded from the study because of the effect of such valvular lesions in altering the hemodynamics of filling.

TABLE I. CLINICAL AND ELECTROKYMOGRAPHIC DATA FROM PATIENTS IN CONGESTIVE FAILURE (WITHOUT DIGITALIS)

NO.	AGE	SEX	DIAGNOSIS*	DYSPNEA	ANKLE EDEMA	DURATION CARDIAC CYCLE (SECONDS)	ISOMETRIC CONTRACTION	EJECTION	TOTAL DIASTOLE	ISOMETRIC RELAXATION PLUS PROTODIASTOLE
1 R. V.	63	M	HCVD	++	0	0.98	0.04	0.22	0.70	0.06
2 P. S.	48	M	HCVD	+++	+	0.51	0.06	0.21	0.30	0.06
3 W.	47	M	HCVD	++	+	0.80	0.04	0.24	0.54	0.06
4 B. C.	64	M	ASHD HCVD	+++	++	1.03	0.08	0.20	0.69	0.05
5 A. D.	75	M	ASHD HCVD	+++	0	0.81	0.04	0.24	0.55	0.10
6 C. M.	51	M	ASHD	+++	0	0.60	—	—	0.33	0.06
7 E. A.	48	F	HCVD	+	+	0.65	0.07	0.22	0.38	0.06
8 H. P.	66	M	ASHD	+	0	0.61	0.08	0.19	0.34	0.16
9 I. C.	63	F	HCVD	++	0	0.50	0.07	0.17	0.28	0.15
10 B. I.	68	F	HCVD ASHD	++++	+	0.65	0.04	0.20	0.36	0.04
11 E. C.	75	M	ASHD	+	++	1.00	0.05	0.28	0.70	0.12
12 L. C.	44	F	HCVD	+++	+	0.72	0.08	0.24	0.44	0.07
13 R. S.	61	M	HCVD	+++	+	0.95	0.05	0.24	0.63	0.06
14 C. M.	67	M	ASHD	++	++	1.02	0.10	0.30	0.63	0.14
15 H. H.	52	M	HCVD	+++	++	0.64	0.08	0.19	0.39	0.08
16 E. J.	80	M	ASHD	+++	+++	0.68	—	—	0.46	0.07
17 W. W.	66	M	HCVD ASHD	+++	++	0.52	0.05	0.17	0.29	0.07
18 N. H.	73	F	HCVD ASHD	+++	++	0.85	0.04	0.26	0.50	0.10
19 W. B.†	72	M	HCVD	+++	++	(Shortest cycle) 0.68	0.04	0.26	0.38	0.12
						(Longest cycle) 1.04	0.04	0.27	0.73	0.12

*ASHD = arteriosclerotic heart disease.

HCVD = hypertensive cardiovascular disease.

†Patient exhibited auricular fibrillation at the time of the tracing. All other patients had sinus rhythm.

The onset of the rapid filling phase in diastole was marked as beginning with the onset of the well-defined upsweep of the curve following isometric relaxation (Fig. 1). This upsweep, signifying an outward movement of the heart border, indicates the beginning of the phase of rapid ventricular filling in diastole, immediately after the opening of the auriculoventricular valves. Measurements of the duration of the remaining phases of the cardiac cycle were made according to methods previously described.[5]

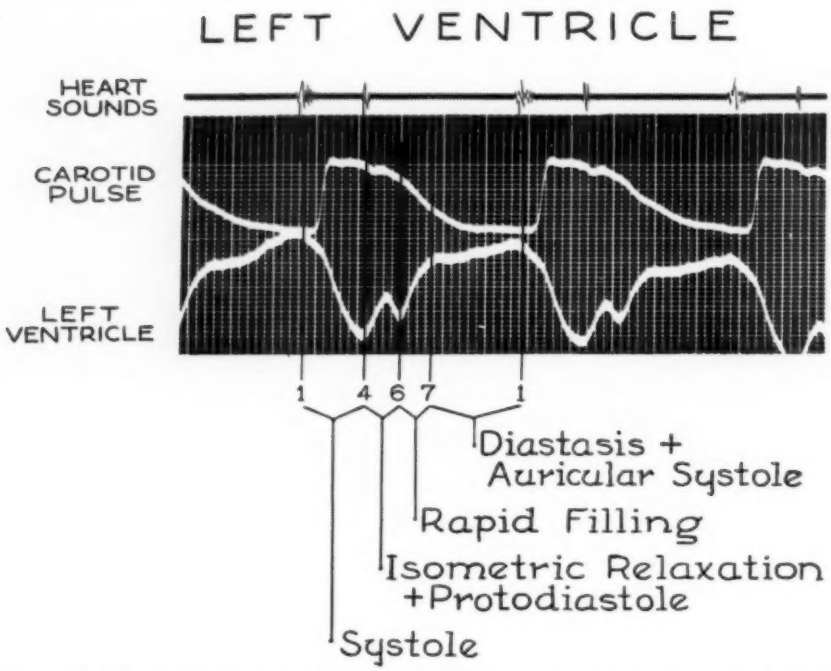

Fig. 1.—An electrokymographic tracing of the left ventricular border with the method of delineating the diastolic phases of the cardiac cycle. Line *1* is drawn from the onset of the first heart sound, line *4* from the onset of the second heart sound. Line *6* is drawn from the onset of the upswing of the filling curve. Line *7* is drawn through the change in gradient of the filling curve, from rapid upswing to flattened curve. The portion of the ventricular (lower) curve between lines *6* and *7* delimits the rapid filling phase, measured in the present study.

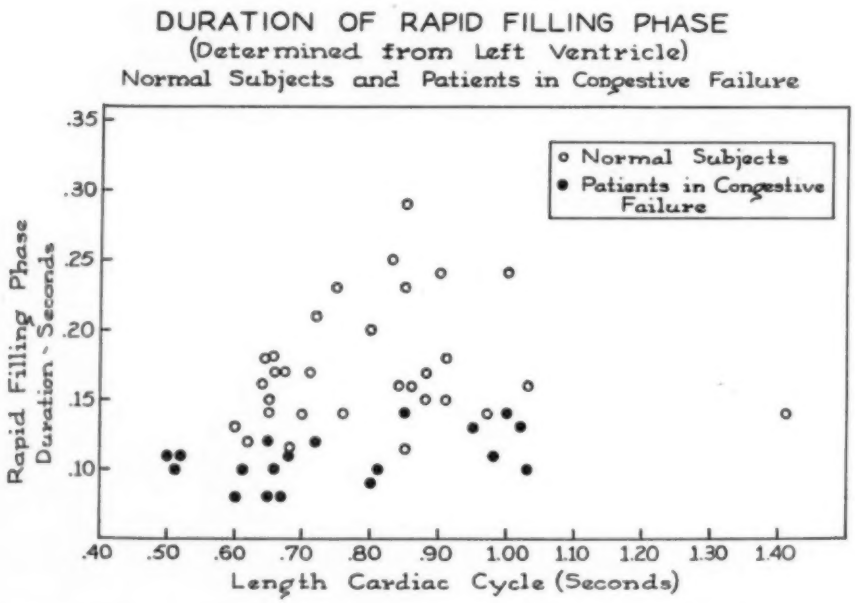

Fig. 2.—Duration of rapid filling in patients in congestive failure and in normal subjects. It will be noted that, as a group, the patients in congestive failure have a shorter rapid filling phase than the normal subjects.

RESULTS

Alterations in the Phase of Rapid Ventricular Filling.—The significant finding in the group of patients with congestive failure was a definite shortening of the phase of rapid filling as compared with the normal subjects. These results are expressed graphically in Fig. 2. It has been noted previously that the rapid filling phase is very little affected by variations in rate in normal subjects.[5] When the patients in congestive failure were studied, there also appeared to be little or no influence of rate on the duration of rapid filling (see Fig. 2). Reference to Table II reveals that the mean duration of rapid filling in the normal group was 0.174 second ±0.043, compared with a mean duration of 0.11 second ±0.019 for the group of patients in failure.

TABLE II. DURATION OF RAPID FILLING PHASE

NORMAL SUBJECTS				CARDIAC PATIENTS	
SUBJECT NO.	DURATION (SECONDS)	SUBJECT NO.	DURATION (SECONDS)	PATIENT NO.	DURATION (SECONDS)
1	0.24	17	0.29	1	0.12
2	0.17	18	0.23	2	0.10
3	0.17	19	0.15	3	0.09
4	0.18	20	0.23	4	0.10
5	0.14	21	0.12	5	0.10
6	0.16	22	0.17	6	0.08
7	0.14	23	0.13	7	0.08
8	0.16	24	0.12	8	0.10
9	0.16	25	0.12	9	0.11
10	0.20	26	0.16	10	0.08
11	0.14	27	0.14	11	0.14
12	0.15	28	0.14	12	0.12
13	0.18	29	0.15	13	0.13
14	0.17	30	0.24	14	0.13
15	0.25	31	0.18	15	0.12
16	0.21			16	0.12
				17	0.11
				18	0.14
				19	0.12

NORMAL SUBJECTS		CARDIAC PATIENTS	
Mean	0.174 second	Mean	0.110 second
Range	0.12 to 0.29 second	Range	0.08 to 0.14 second
Standard deviation of mean	±0.0078 second	Standard deviation of mean	±0.004 second
Standard deviation of individual measurement	±0.043 second	Standard deviation of individual measurement	±0.019 second
Probable error of mean	±0.0053 second	Probable error of mean	±0.003 second
Probable error of individual measurement	±0.029 second	Probable error of individual measurement	±0.012 second

No significant marked changes in contour or gradation of the filling phase could be noted in these patients, although occasionally the rapid filling phase appeared to be more abrupt in its upward excursion in the presence of congestive failure than it was in the normal subjects. In other cases the contour seemed

somewhat altered in that the prolonged and marked definite upward sweep of rapid filling was abbreviated. The upward excursion was also sometimes much diminished in subjects suffering from congestive failure. So far as the general contour of the tracings alone was concerned, however, no constant and pathognomonic changes could be seen in the diseased group.

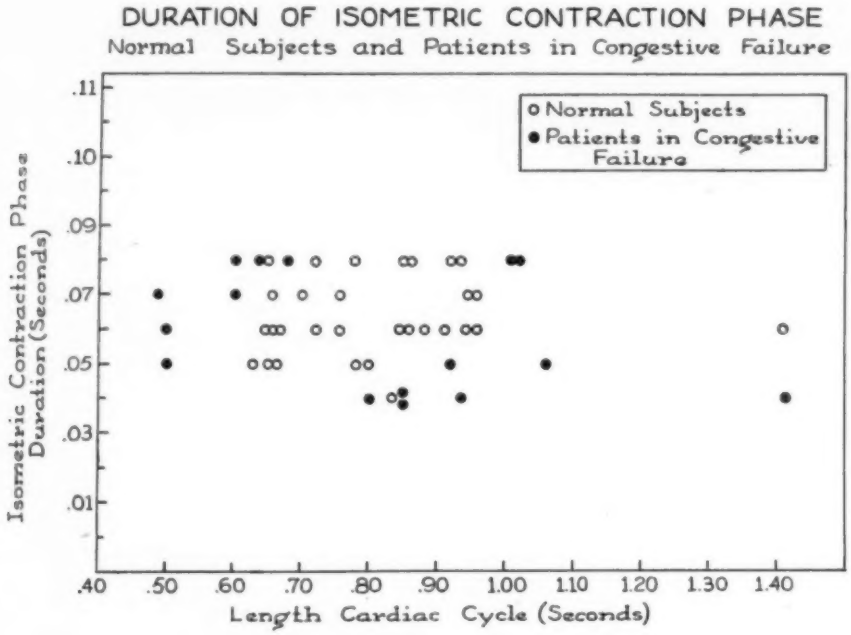

Fig. 3.—Duration of isometric contraction phase in patients in congestive failure and in normal subjects. The patients in congestive failure did not appear to have isometric contraction periods that were significantly different from the normal subjects. (These measurements were made from the aortic knob and are slightly longer than measurements made from the ascending aorta.[5] This slight prolongation, 0.01 to 0.015 second, probably represents transmission time from the aortic valve to the aortic knob.[5])

Phases of Isometric Contraction and Ejection.—The phase of isometric contraction, as will be seen in Fig. 3, was not significantly different in duration in the patients with congestive failure as compared with the normal subjects. The duration of the ejection phase (Fig. 4) also failed to show any apparent difference in duration in the cardiac patients in comparison with the normal group. The duration of the isometric contraction phase appeared to be independent of cycle length. However, there was a tendency for the ejection phase to lengthen with longer cycle lengths in both the normal and diseased groups. A careful study of the contour and appearance of the isometric contraction and ejection phases in the two groups failed to disclose any unusual alterations or pathognomonic patterns that could easily be used to differentiate the two groups.

The Phases of Protodiastole and Isometric Relaxation.—Protodiastole, the earliest phase of diastole (Fig. 1), during which time the pressure drops sharply in the ventricle and aorta, often cannot be measured accurately from the ven-

tricular tracing because of technical difficulties. The same applies to the succeeding phase of isometric relaxation, during which phase the semilunar and atrioventricular valves are closed. However, previous studies have indicated that these phases can be measured together, as a unit, from electrokymographic tracings of the ventricle.[5] Fig. 5 shows that the combined duration of these two earliest phases of diastole was not greatly different in the cardiac patients and normal subjects, although a tendency for shortening of these combined phases appeared in some of the patients with congestive failure.

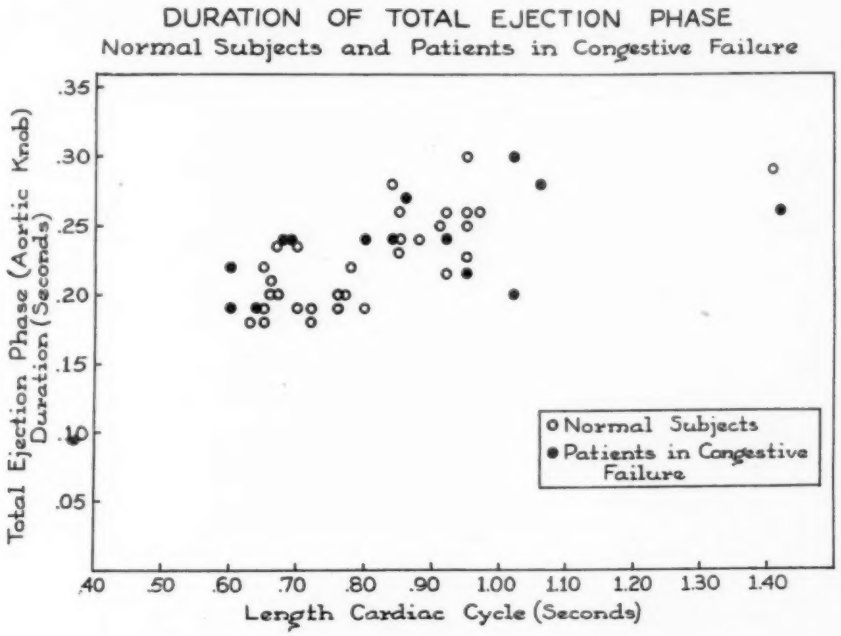

Fig. 4.—Duration of total ejection phase in patients in congestive failure and in normal subjects. No significant difference in duration of the ejection phase was noted in the two groups. There is a slight tendency in both the cardiac patients and in the normal subjects for the ejection phase to lengthen with longer cycle lengths.

DISCUSSION

From the data presented, it appears that the presence of congestive failure is accompanied by a definite shortening of the phase of rapid filling as compared with the duration of this phase in normal subjects. Except in the case of mitral stenosis with cardiac failure,[6] where filling proceeds throughout the whole phase of diastole, the rapid filling phase can be regarded as the time interval during which the greatest portion of blood enters the ventricle,[7,8] both in normal subjects and in patients suffering from congestive failure. It has also been previously shown, in electrokymographic studies in human subjects, that the duration of the rapid filling phase is relatively little affected by moderate changes in cardiac rate.[5] Shortening of this phase has generally been found to occur only with marked increases in heart rate, with extremely short periods of diastole.[7,8] From

Fig. 2, it will be seen that the heart rate (as determined from duration of the cardiac cycle) in the group of patients with congestive failure is, in general, not significantly different from the group of normal subjects. The observed shortening of the rapid filling phase therefore cannot be accounted for by an increase in heart rate alone.

In seeking an explanation of the cause for shortening of the rapid filling phase in congestive failure, it is necessary to consider the pressure relationships that obtain in early diastole in both health and disease. Under normal conditions, intracardiac catheterization studies reveal that with the onset of ventricular diastole the pressure within the ventricles falls abruptly, generally reaching a level near the atmospheric level or a few millimeters below this level.[9-11]

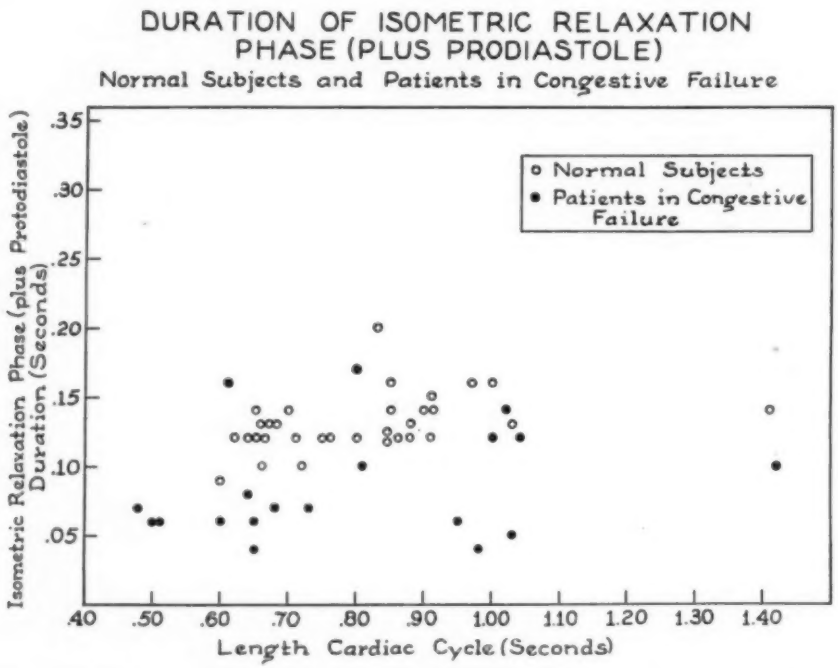

Fig. 5.—Duration of isometric relaxation phase, plus protodiastole, in patients in congestive failure and in normal subjects. No marked differences are noted in the patients in congestive failure and normal subjects. A slight tendency to shortening of the duration of these combined phases is noted in the patients with cardiac disease.

This fall produces an early "diastole dip" in the ventricular pressure level in the early phase of diastole.* [9-11] At the moment the ventricular pressure falls below the auricular level, the atrioventricular valves open and blood rushes rapidly into the ventricle. The intra-auricular pressure level at this time in normal subjects has generally been found to be only a few millimeters above that in the ventricle.[9-11] Thus, under normal circumstances, at the time of opening of the

*This early diastole fall in intraventricular pressure has also been observed in animals by Katz and associates.[12,13,14] As a result of their investigations it also appears that this fall is not due to an artifact, but is an authentic record of the ventricular pressure changes occurring at this moment.

atrioventricular valves, in the earliest phase of diastole, the atrioventricular pressure filling gradient is only a few millimeters of mercury. With atrioventricular valvular opening the auricular and ventricular pressures rapidly equalize and reach a state of equilibrium, filling then proceeding more slowly during the remainder of diastole. Ventricular filling, therefore, is dependent primarily upon the pressure difference existing between the auricle and ventricle. Furthermore, the facility with which filling occurs in early diastole appears to bear a relationship to the magnitude of this atrioventricular pressure gradient.[3,15,16] In this connection it is worthy of note that in the original communication of Patterson, Piper, and Starling[3] an increased venous pressure was found to produce a more rapid inflow from auricle to ventricle in the heart-lung preparation.

In the presence of established congestive heart failure, catheterization studies have shown that significant alterations occur in the pressure filling gradient.[9-11] Thus, both peripheral venous and auricular pressures are increased, and the filling gradient from periphery to auricle is reduced or even reversed for short periods. Furthermore, although the intra-auricular (filling) pressure is markedly *increased* in the presence of failure, the *initial* diastolic intraventricular pressure, existent at the time of opening of the atrioventricular valves, is usually approximately atmospheric or below. Indeed, under certain conditions this early diastolic decline in intraventricular pressure has been found to be slightly more marked in patients in failure than in normal subjects.[9-11] Hence, the effective auriculoventricular pressure filling gradient in the earliest phase of diastole is markedly increased in the presence of congestive failure compared to the gradient existent in normal hearts. Filling thus occurs with greater ease and rapidity in this early diastolic phase of rapid ventricular filling.

Immediately after the initial increase of blood, the pressures within the auricle and ventricle rapidly reach a state of equilibrium and become approximately equal. Moreover, in this latter phase of diastole, the ventricular and auricular pressures are elevated above normal levels in the presence of congestive failure.

From these considerations, the observed shortening of the rapid filling phase in congestive failure is readily understandable. Although the existence of the high pressure filling gradient and the marked "diastolic dip" of ventricular pressure, as well as the rapid initial inflow of blood from the auricle, have been noted by others,[9-14] their total effect upon the duration of rapid filling has not previously been fully appreciated. The increased rapidity of rapid filling in congestive failure observed in the present study, therefore, would appear to be related primarily to the increased pressure filling gradient present in the failing heart at the onset of ventricular diastole. As a measure of the abnormal hemodynamics present in diseased hearts, the systematic recording of the duration of the rapid filling phase (at rest) and its comparison with normal values would therefore appear to be of objective value in assessing the presence of an increased atrioventricular pressure filling gradient due to heart failure.

The failure of this study to show significant alterations in the duration of systole and its phases, including isometric contraction and ejection, indicates that myocardial insufficiency with congestive failure, as observed clinically, is

not accompanied by hemodynamic alterations which cause significant changes in the duration of the various phases of contraction of the heart muscle.

SUMMARY

Electrokymographic studies were made of the duration and contour of the various phases of the cardiac cycle in systole and diastole in a series of nineteen patients suffering from nonvalvular congestive heart failure. A comparison with similar observations in a group of thirty-one normal subjects revealed that significant alterations in the length of the various phases occurred only in the period of rapid filling. The duration of the rapid filling phase was definitely shortened in the patients with cardiac disease. No significant changes in the duration or contour of the phases of isometric contraction or ejection were found. The possible causes for the observed shortening of the rapid filling phase in congestive failure are discussed. The presence of an increased atrioventricular pressure filling gradient appears best to explain this observed shortening. By contrast, no change in the time relationships of the various phases of systole were observed in the cardiac patients as compared with those in normal subjects.

REFERENCES

1. Huckabee, Wm., Casten, G., and Harrison, T. R.: Experimental Hypervolemic Heart Failure: Its Bearing on Certain General Principles of Heart Failure, Circulation **1**:343, 1950.
2. Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Effects of Venesection in Low Output Heart Failure, Clin. Sc. **6**:41, 1946.
3. Patterson, S. W., Piper, H., and Starling, E. H.: The Regulation of the Heart Beat, J. Physiol. **48**:465, 1914.
4. Henny, G. C., Boone, B. R., and Chamberlain, W. E.: Electrokymograph for Recording Heart Motion, Improved Type, Am. J. Roentgenol. **57**:409, 1947.
5. Willis, K., Eddleman, E. E., Jr., Acker, J., Poulos, E., and Heyer, H. E.: Variations in the Duration of Phases of the Cardiac Cycle in Normal Hearts as Studied by the Electrokymograph, AM. HEART J. **40**:485, 1950.
6. Gorlin, R., Lewis, B. M., Haynes, F. W., Spiegl, R. J., and Dexter, L.: Factors Regulating Pulmonary "Capillary" Pressure in Mitral Stenosis. IV, AM. HEART J. **41**:834, 1951.
7. Henderson, Y.: Volume Curve of the Ventricles of the Mammalian Heart and the Significance of This Curve in Respect to the Mechanics of the Heart Beat and the Filling of the Ventricles, Am. J. Physiol. **16**:325, 1906.
   Henderson, Y.: Acapnia and Shock. II. A Principle Underlying the Normal Variations in the Volume of the Blood Stream, and the Deviation From This Principle in Shock, Am. J. Physiol. **23**:345, 1909.
8. Wiggers, C. J.: Physiology in Health and Disease, ed. 5, Philadelphia, 1949, Lea & Febiger.
9. Bloomfield, R. H., Lauson, J. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of Right Heart Pressures in Normal Subjects and in Patients With Chronic Pulmonary Disease and Various Types of Cardio-circulatory Disease, J. Clin. Investigation **25**:639, 1946.
10. Richards, D. W., Jr.: Cardiac Output by the Catheterization Technique in Various Clinical Conditions, Federation Proc. **4**:215, 1945.
11. Richards, D. W., Jr.: Contributions of Right Heart Catheterization to the Physiology of Congestive Heart Failure, Am. J. Med. **3**:434, 1947.
12. Katz, L. N.: The Role Played by the Ventricular Relaxation Process in Filling the Ventricle, Am. J. Physiol. **95**:542, 1930.
13. Brams, W. A., and Katz, L. N.: Studies on the Overdistended Heart. I. Effects of Venesection, Am. J. Physiol. **98**:556, 1931.
14. Katz, L. N., and Brams, W. A.: Studies on the Overdistended Heart. II. The Role of Relaxation in Filling the Distended and Overdistended Heart, Am. J. Physiol. **98**:569, 1931.
15. Wiggers, C. J., and Katz, L. N.: Contour of the Ventricular Volume Curves Under Different Conditions, Am. J. Physiol. **58**:439, 1922.
16. Wiggers, C. J.: Determinants of Cardiac Performance, Circulation **4**:485, 1951.

WATER AND ELECTROLYTE CONTENT OF CARDIAC AND SKELETAL MUSCLE IN HEART FAILURE AND MYOCARDIAL INFARCTION

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METABOLIC studies of water and electrolytes, carried out on patients during their recovery from congestive heart failure, demonstrated an uptake of potassium and sodium and a release of water by the cells.[1] From these findings, it was postulated that, during the development of cardiac failure, the cells lost potassium and sodium and gained water, presumably because of activation of osmotically inert cellular base.

The present study is a part of a series on water and electrolyte metabolism in congestive failure. Its purpose is to compare the water and electrolyte content of myocardial and skeletal muscle obtained at autopsy from patients dying of congestive failure or myocardial infarction with the composition of specimens obtained from patients dying of noncardiac causes.

The material comprised forty-seven cases. In its selection, care was taken to eliminate patients with uremia, diabetic acidosis, or other metabolic disease likely to cause alterations in the composition of myocardium or skeletal muscle independent of cardiac disease.

The patients were classified from a clinicopathologic standpoint into the following groups: I, controls, comprising sixteen patients with normal hearts at autopsy and no evidence of a metabolic disorder; II, uncomplicated left ventricular hypertrophy, found in fourteen patients who showed no evidence of congestive failure, received no cardiac glycosides during hospitalization, and died of noncardiac causes; III, congestive failure with underlying left ventricular hypertrophy, present during hospitalization and at autopsy in eight patients despite digitalization; and IV, acute myocardial infarction, responsible for death in seven patients.

METHOD

Heart muscle blocks were obtained during autopsy from four standard sites in the left ventricle: (1) anterior-apical, (2) mid-septal, (3) mid-lateral, and (4) posterior basal. In Group IV separate blocks were taken from areas of acute

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TABLE I. GROUP I—CONTROL

CASE	HEART MUSCLE (PER 100 GM. OF WET TISSUE)						SKELETAL MUSCLE (PER 100 GM. OF WET TISSUE)					
	H_2O (GM.)	Na (MEQ.)	K (MEQ.)	cl (MEQ.)	Mg (MEQ.)	P (MEQ.)	H_2O (GM.)	Na (MEQ.)	K (MEQ.)	cl (MEQ.)	Mg (MEQ.)	P (MEQ.)
1	80.1	5.13	9.75	4.67	0.435	4.10	80.2	6.50	6.00	5.66	0.302	2.76
2	79.3	4.86	9.55	4.27	0.345	3.80	78.3	3.34	12.00	3.27	0.369	3.40
3	81.3	4.82	10.72	4.33	0.441	4.35	77.9	3.08	10.60	2.73	0.405	3.90
4	79.4	4.91	8.03	4.00	0.450	4.10	75.3	3.74	10.40	2.61	0.465	4.08
5	77.9	4.00	8.98	3.91	0.605	5.37	74.4	2.78	10.10	2.28	0.495	4.60
6	79.8	4.90	8.00	4.03	0.456	3.47	77.5	3.34	10.45	2.17	0.457	3.01
7	78.6	4.21	8.55	3.13	0.416	2.80	79.1	2.38	6.63	1.88	0.510	2.80
8	78.0	5.05	9.70	3.85	0.348	3.82	75.8	4.13	14.50	2.39	0.350	5.38
9	78.5	5.38	7.40	4.20	0.437	4.53	79.0	5.69	4.75	3.69	0.395	3.09
10	78.4	5.21	7.76	4.16	0.495	2.96	76.6	4.05	9.78	3.01	0.467	3.14
11	79.3	5.73	7.96	3.83	0.498	3.40						
12	78.5	5.90	6.90		0.422	4.15	74.6	5.65	8.40		0.465	4.87
13	80.2	4.82	8.19		0.435	3.67						
14	77.7	4.65	7.20									
15	78.1	3.65	7.38									
16	76.1	6.17	7.11									
Mean	78.8	4.96	8.32	4.04	0.445	3.88	77.2	4.06	9.42	2.97	0.425	3.72
Standard deviation	±1 .2	±0.60	±1.09	±0.37	±0.060	±0.65	±1.9	±1.26	±2.65	±1.00	±0.063	±0.86

myocardial infarction and from distant areas that appeared uninfarcted to gross examination. Skeletal muscle blocks were secured from the pectoralis major. Fibrous and fatty tissues were trimmed off, and the inner portions of these blocks were analyzed for water, sodium, and potassium in all samples and, in addition, for chloride, magnesium, and phosphorus in the majority of the cases.

Water content was determined gravimetrically by vacuum desiccation under constant temperature of 100° C., using the Abderhalden apparatus. Sodium, potassium, magnesium, and phosphorus were analyzed by a modification of the spectrographic method for plasma and urine, after digestion of the dried samples with nitric acid-perchloric acid mixture.[2] In those specimens analyzed for sodium and potassium only, the flame photometer was employed.[3] Chloride content was determined by the Volhard titration method after digestion of a wet sample with 5 N sodium hydroxide.

RESULTS

The values for water are reported in grams per 100 Gm. of wet tissue, those for sodium, potassium, magnesium, phosphorus, and chloride in milliequivalents per 100 Gm. of wet tissue. One milliequivalent of phosphorus represented 55.8 mg. of the element.[4] Tables I, II, III, and IV give the results in each individual case of the four respective groups. Since no consistent difference in the composition of myocardium from the four standard sites was found in the absence of infarction, the values for cardiac muscle in Tables I, II, and III represent averages of the analyses of four separate blocks. In Table IV the values for infarcted myocardium and grossly normal myocardium are recorded separately for each case. Table V summarizes the results of each group.

DISCUSSION

Group I. Controls (Table I).—Since autopsy material from accidental deaths was not available to us, the control group was selected from patients who had died suddenly from diseases such as ruptured cerebral aneurysm or who had succumbed to brief illnesses, unattended by any obvious disturbance of fluid and electrolyte balance. The sixteen hearts classified into the control group were normal to gross and microscopic examination and served as the index of the normal in fluid and electrolyte content, subject to the reservation that unpredictable chemical alterations may have occurred during the agonal state in the absence of histologic changes. In spite of possible agonal alterations in chemical composition, the results were in good agreement with those reported in the literature. The average values per 100 Gm. of wet cardiac muscle in our sixteen cases were as follows: water 78.8 ± 1.2 Gm.; sodium 4.96 ± 0.60 meq.; potassium 8.32 ± 1.09 meq.; chloride 4.04 ± 0.37 meq.; magnesium 0.445 ± 0.06 meq.; and phosphorus 3.88 ± 0.65 meq. These figures were almost identical with the mean values in five cases reported by Wilkins and Cullen,[5] who found 78.9 Gm. of water, 4.0 meq. of sodium, 7.8 meq. of potassium, 0.42 meq. of magnesium, and 3.65 meq. of phosphorus per 100 Gm. of wet tissue. The authors did not analyze for chloride. Myocardial analyses in thirteen cases of accidental death reported

by Mangum and Myers[6] gave average values of 80.8 Gm. of water, 7.1 meq. of potassium, and 3.47 meq. of phosphorus per 100 Gm. The mean potassium content of five normal hearts analyzed in Harrison's laboratory[7,8] was 7.57 meq. per 100 Gm. of wet tissue. The values obtained by Herrmann and Decherd[9] and Scott[10] in cardiac patients without congestive failure were significantly lower, perhaps because these cases did not actually represent normal controls.

The average values for magnesium and phosphorus in skeletal muscle were comparable to those in the myocardium, but water, sodium, and chloride content was lower, whereas potassium content was higher. Our findings in respect to water and potassium confirmed early work in Harrison's laboratory.[7,8] From a study of the results in individual cases in Table I, it would appear that magnesium contents of skeletal and cardiac muscle were comparable in most instances, whereas sodium, potassium, and chloride contents were neither comparable nor parallel. Skeletal muscle was subject to greater variation in water, sodium, potassium, and chloride content than the myocardium.

The foregoing differences in chemical composition were believed referable chiefly to differences in partition of water between the muscle cell and interstitial space and in small part to differences in fat content. A rough estimate of the partition of water was made by the method of Newburgh[11] on the assumption that practically all chloride was extracellular and that the concentration in the interstitial water amounted to 117 meq. per liter. Fat content of cardiac muscle was negligible and therefore disregarded, whereas that of skeletal muscle was estimated at 1 Gm. per 100 Gm. of wet tissue. Estimates of the partition of water in myocardium, made with the foregoing premises, were as follows: 32.6 Gm. of extracellular and 46.2 Gm. of intracellular water per 100 Gm. of wet tissue, whereas the corresponding estimates for distribution of water in skeletal muscle were 23.5 Gm. in the interstitial space and 53.7 Gm. within the cells. Although the validity of these figures depends upon the accuracy of the assumptions employed in the calculations, it is noteworthy that the estimated partition in these cases is in accord with derived figures obtained by others from analyses of animal muscle[12] and biopsied human skeletal muscle.[13]

The intracellular concentrations of base were estimated on the assumption that the concentrations in interstitial fluid were 143 meq. per liter for sodium, 4.0 meq. per liter for potassium, and 3 meq. per liter for magnesium. The values for cardiac muscle, expressed in milliequivalents per liter of intracellular water, were sodium 6.3, potassium 177.0, and magnesium 7.7; the corresponding figures for skeletal muscle were sodium 13.1, potassium 174.0, and magnesium 6.8. The higher intracellular concentration of sodium in skeletal muscle compensated for the lower concentrations of potassium and magnesium, so that the concentrations of total base were essentially the same in cardiac and skeletal muscle.

Since there is no satisfactory unit available to indicate the number of cells actually present per 100 Gm. of wet tissue, it is necessary to consider the cells collectively. Obviously the total water content of 100 Gm. of wet tissue or the calculated distribution of extracellular and intracellular water reflects in no way the absolute quantity of water in each individual cell or the relative quantity of water in the extracellular compartment per unit number of cells.

TABLE II. GROUP II—UNCOMPLICATED LEFT VENTRICULAR HYPERTROPHY

CASE	HEART MUSCLE (PER 100 GM. OF WET TISSUE)						SKELETAL MUSCLE (PER 100 GM. OF WET TISSUE)					
	H_2O (GM.)	Na (MEQ.)	K (MEQ.)	Cl (MEQ.)	Mg (MEQ.)	P (MEQ.)	H_2O (GM.)	Na (MEQ.)	K (MEQ.)	Cl (MEQ.)	Mg (MEQ.)	P (MEQ.)
17	77.4	5.26	9.37	4.65	0.480	3.97	75.4	3.96	10.70	4.00	0.465	4.00
18	78.0	4.91	8.30	4.13	0.500	4.43	72.3	3.44	10.40	2.54	0.618	5.51
19	77.6	4.57	7.82	3.66	0.450	3.30	74.0	3.83	9.59	2.09	0.501	3.61
20	78.8	5.30	9.26	4.80	0.438	3.48	77.6	4.35	10.61	3.78	0.394	2.75
21	79.6	4.79	8.10	3.43	0.425	3.71	75.7	3.40	12.62	2.40	0.486	4.52
22	77.1	5.18	6.50	4.75	0.475	3.33	77.3	3.60	13.90	2.20	0.613	3.92
23	75.9	5.00	8.65	4.00	0.495	4.20	75.2	4.00	12.39	3.19	0.483	4.49
24	78.8	7.61	8.53	5.22	0.445	3.09	77.1	4.56		2.82	0.649	4.76
25	79.4	4.48	7.45	3.52	0.420	3.70						
26	76.1	4.53	8.95									
27	77.0	4.57	7.55									
28	76.8	4.09	8.30									
29	75.5	4.40	8.53									
30	78.7	4.30	7.88									
Mean	77.6	4.93	8.23	4.24	0.459	3.69	75.6	3.89	11.46	2.88	0.526	4.20
Standard deviation	±1.3	±0.67	±0.75	±0.60	±0.028	±0.41	±1.9	±0.39	±1.44	±0.67	±0.084	±0.77

TABLE III. GROUP III—HYPERTROPHIED, DIGITALIZED, CONGESTIVE HEART FAILURE

CASE	HEART MUSCLE (PER 100 GM. OF WET TISSUE)						SKELETAL MUSCLE (PER 100 GM. OF WET TISSUE)					
	H_2O (GM.)	Na (MEQ.)	K (MEQ.)	cl (MEQ.)	Mg (MEQ.)	P (MEQ.)	H_2O (GM.)	Na (MEQ.)	K (MEQ.)	cl (MEQ.)	Mg (MEQ.)	P (MEQ.)
36	80.4	5.49	6.90	5.05	0.398	3.68	76.6	3.44	7.58	4.50	0.361	3.13
37	80.6	4.00	6.65	2.76	0.460	3.90	80.5	3.05	6.65	2.45	0.404	3.68
38	78.1	5.61	6.45	4.26	0.394	3.55	70.6	3.00	7.70	2.20	0.343	3.12
39	79.2	4.83	6.90	4.26	0.435	4.00	72.6	4.00	7.38	2.87	0.414	4.22
40	80.5	5.90	6.90	4.26	0.385	3.86						
41	78.4	4.35	7.70				73.6	4.33	9.80			
42	77.8	5.49	5.75									
43	76.0	6.90	6.98									
Mean	78.9	5.32	6.78	4.12	0.414	3.80	74.8	3.56	7.82	3.00	0.380	3.53
Standard deviation	±2.3	±0.86	±0.51	±0.56	±0.063	±0.16	±3.4	±0.52	±1.06	±0.90	±0.030	±0.45

Group II. Uncomplicated Left Ventricular Hypertrophy Without Digitalization or Congestive Failure (*Table II*).—The myocardial water and electrolyte content in uncomplicated left ventricular hypertrophy was almost identical with that in the control group, as shown by a comparison of the mean figures in the first two tables. Thus the average values for hypertrophied and normal myocardium, respectively, were water 77.6 ± 1.3 Gm. and 78.8 ± 1.2 Gm.; sodium 4.93 ± 0.67 meq. and 4.96 ± 0.60 meq.; potassium 8.23 ± 0.75 meq. and 8.32 ± 1.09 meq.; chloride 4.24 ± 0.60 meq. and 4.04 ± 0.37 meq.; magnesium 0.459 ± 0.028 meq. and 0.445 ± 0.060 meq.; and phosphorus 3.69 ± 0.41 meq. and 3.88 ± 0.65 meq. per 100 Gm. of wet tissue. Myers[14] correlated myocardial potassium and phosphorus with cardiac weight. His data showed a fairly constant phosphorus content over a wide range of weights and no significant difference in the potassium content of normal and moderately hypertrophied hearts, weighing up to 530 grams, but a reduction in potassium in hearts exceeding 550 grams. Since his data gave no clear indication as to whether or not patients with congestive failure of milder grade or terminal development were excluded from the series, the lower potassium content of markedly hypertrophied hearts may have been related to the greater incidence of congestive failure in this group.

Group III. Congestive Failure With Underlying Left Ventricular Hypertrophy (*Table III*).—Cardiac muscle from patients dying in congestive failure showed a significant decrease in potassium content to an average of 6.78 ± 0.51 meq. per 100 Gm., as compared with values of 8.32 ± 1.09 meq. in controls and 8.23 ± 0.75 meq. in uncomplicated left ventricular hypertrophy. These findings confirmed reports of other workers.[5,7,8,14] On the other hand, our data revealed no significant change in content of water, sodium, chloride, magnesium, and phosphorus in the failing cardiac muscle as compared with the normal or the hypertrophied, but compensated, myocardium.

Since all our patients with congestive failure received a cardiac glycoside during hospitalization, it was necessary to consider digitalis action as a possible causative or contributory factor in the lowering of myocardial potassium. Studies in animals[15-18] have shown that toxic doses of digitalis reduce myocardial potassium, whereas therapeutic doses cause no significant change. Inasmuch as none of the patients was clinically overdigitalized at the time of death, it was concluded that the lowering of myocardial potassium was associated with congestive failure per se, rather than with the digitalis employed in treatment. This conclusion is supported by more recent studies in another local hospital,[19] demonstrating reduction in myocardial potassium in patients who died in congestive failure without having received any cardiac glycoside.

Skeletal muscle potassium was also lower in patients with congestive failure than in controls or in the group with uncomplicated left ventricular hypertrophy. The parallelism in the fall of potassium in cardiac and skeletal muscle with congestive failure suggests that the decrease is the result, rather than the cause, of failure.

The question arose as to whether the drop in potassium content without significant change in total water reflected a decrease in concentration of potassium

in the cells or merely an increase of extracellular fluid at the expense of intracellular fluid. Accordingly, estimates of water and electrolyte partition were made in the same manner as in the control group, similar values for the extracellular concentrations of each electrolyte being assumed.* The derived values per 100 Gm. of cardiac muscle were 33.4 Gm. of extracellular water and 45.5 Gm. of intracellular water; those for 100 Gm. of skeletal muscle from patients with congestive failure were 23.6 Gm. of extracellular water and 50.7 Gm. of intracellular water. The estimated partition of water in cardiac and skeletal muscle of patients with congestive failure did not differ significantly from that in the corresponding type of muscle from the control group.

The estimated concentrations of intracellular base in decompensated myocardium were as follows: sodium 12.1 meq., potassium 146 meq., and magnesium 6.85 meq. per liter of intracellular water. Comparison of these values with the corresponding figures in the control group showed a significantly lower intracellular potassium, a very slightly lower magnesium, and a higher sodium concentration in decompensated myocardium. The total intracellular base concentration was significantly reduced below the control value of 191 meq. per liter to 164 meq. per liter.

The intracellular concentrations in skeletal muscle from patients in congestive failure, estimated in the same manner, were as follows: sodium 3.9 meq., potassium 152 meq., and magnesium 6.2 meq. per liter of intracellular water. The values for sodium and potassium were lower and those for magnesium almost the same as the concentrations in skeletal muscle from the control group. The total intracellular base concentration in skeletal muscle from patients in congestive failure was significantly reduced below the control value of 193.9 meq. per liter to 162.1 meq. per liter. It was pointed out previously that the total intracellular base concentration of skeletal muscle from the control group (193.9 meq. per liter) was almost identical with that of myocardium from the same patients (191 meq. per liter). Attention is now drawn to the fact that the total intracellular base concentration of skeletal muscle from patients with congestive failure (162.1 meq. per liter) was almost identical with that of the decompensated myocardium (164 meq. per liter), indicating comparable losses of base from skeletal and cardiac muscle during congestive failure.

The parallelism in the reduction of the concentrations of total intracellular base and potassium in skeletal and cardiac muscle during failure suggests that serial biopsies of skeletal muscle during life might serve as a useful, though indirect, index of changes in the concentration of total base and potassium in the myocardium. Furthermore, the reduction in total base and potassium of myocardial and skeletal muscle found in congestive failure confirms that previously postulated[1] on the basis of demonstrated cellular uptake during recovery from cardiac decompensation.

The significantly higher concentration of total base in intracellular than in extracellular fluid of the control group indicates either that part of the intra-

*It is recognized that errors in calculations are more likely to occur in the group with congestive failure than in the controls because of the tendency for mercurial diuretics employed in the treatment of cardiac failure to depress plasma chlorides and sodium below the assumed concentrations.

cellular electrolyte is normally bound in an osmotically inactive complex or that nondiffusable tissue protein creates sufficient osmotic imbalance to produce Donnan's effect. In congestive failure, the normal difference in the concentrations of total base in intracellular and extracellular fluid is reduced or obliterated. The reduction in concentration of total cellular base associated with congestive failure may result from either (1) activation of inert base, necessitating release of electrolyte from the cell to preserve osmotic equilibrium with the interstitial fluid, or (2) breakdown of tissue protein with consequent reduction in the Donnan effect.

Group IV. Recent Myocardial Infarction (*Table IV*).—Comparison of the average values obtained from the analysis of grossly infarcted myocardial blocks from Group IV with the normal averages from Group I showed a reduction in potassium and magnesium content to approximately one-half of the control values, a decrease in phosphorus to approximately 60 per cent of the control, and a marked elevation in sodium and chloride. The increase in the latter elements, expressed in milliequivalents per 100 Gm. of wet tissue, over the average control value was 3.15 for sodium and 3.29 for chloride, suggesting that these elements entered infarcted myocardium as neutral sodium chloride. Since there was no significant change in total water, the marked elevation in chloride and sodium reflected, in part, an increase in extracellular fluid at the expense of intracellular fluid and perhaps, in part, a diffusion into dead or dying cells. The postulated increase in extracellular fluid can be confirmed by histologic evidence of severe interstitial edema. Calculation of extracellular and intracellular distribution of water and electrolyte was not made because of the lack of data on the amount of chloride entering dead and dying cells.

The losses of potassium and magnesium amounted to an average of 4.36 meq. per 100 Gm. of wet tissue and therefore preponderated over the gain in sodium, with consequent decrease in total base. The reduction in potassium and magnesium could not have been explained solely by the interstitial edema, even if all chloride remained extracellular. The depletion of potassium, magnesium, and phosphorus was undoubtedly caused primarily by myocardial injury, and the content, expressed in terms of 100 Gm. of wet tissue, was further reduced by the complicating interstitial edema.

It is noteworthy that blocks taken from distant areas that did not show evidence of infarction on gross examination gave results for all five electrolytes that were intermediate between the values obtained from infarcted segments and those from normal controls. These changes were not attributable to congestive failure, since both the reduction in potassium, magnesium, and phosphorus and the elevation in sodium and chloride were greater than the deviations found in congestive failure without infarction. It is probable that acute ischemia without necrosis was responsible for the chemical changes in areas beyond the gross infarct.

The composition of skeletal muscle from patients dying of myocardial infarction corresponded more closely with that of control subjects dying of noncardiac causes than with that of patients dying of congestive failure.

TABLE IV. GROUP IV—ACUTE MYOCARDIAL INFARCTION

CASE	HEART MUSCLE (PER 100 GM. OF WET TISSUE)						SKELETAL MUSCLE (PER 100 GM. OF WET TISSUE)					
	H_2O (GM.)	Na (MEQ.)	K (MEQ.)	cl (MEQ.)	Mg (MEQ.)	P (MEQ.)	H_2O (GM.)	Na (MEQ.)	K (MEQ.)	cl (MEQ.)	Mg (MEQ.)	P (MEQ.)
A. Non-infarcted segments												
44	78.9	7.20	5.95	5.97	0.340	2.96	67.6	4.40	9.57	3.40	0.390	3.30
45	78.8	7.20	4.60	5.80	0.331	3.35	75.5	3.61	11.00	2.40	0.452	2.53
46	78.6	6.52	5.90	5.75	0.230	3.37	76.6	2.91	10.30	2.03	0.500	4.48
47	76.7	7.69	5.30									
48	78.4	4.82	6.88				73.2	2.26	8.16			
49	76.4	8.70	6.00									
50	76.5	5.69	6.77									
Mean	77.8	6.68	5.91	5.84	0.300	3.23	73.2	3.29	9.76	2.61	0.447	3.47
Standard deviation	±1.1	±1.20	±0.74	±0.10	±0.050	±0.17	±3.5	±0.79	±1.05	±0.57	±0.045	±0.80
B. Infarcted segments												
44	77.9	7.51	5.37	7.50	0.198	2.15						
45	79.6	7.95	3.93	7.10	0.294	2.65						
46	78.3	8.40	2.44	7.40	0.154	2.15						
47	76.6	9.00	3.20									
48	77.4	7.70	2.75									
49	70.6	11.59	4.85									
50	77.3	4.60	6.80									
Mean	76.7	8.11	4.19	7.33	0.215	2.32						
Standard deviation	±2.7	±1.96	±1.48	±0.16	±0.058	±0.24						

TABLE V. SUMMARY

GROUP	H_2O	Na	K	Cl	Mg	P
			Heart Muscle			
I	78.8 ± 1.2	4.96 ± 0.60	8.32 ± 1.09	4.04 ± 0.37	0.445 ± 0.060	3.88 ± 0.65
II	77.6 ± 1.3	4.93 ± 0.67	8.23 ± 0.75	4.24 ± 0.60	0.459 ± 0.028	3.69 ± 0.41
III	78.9 ± 2.3	5.32 ± 0.86	6.78 ± 0.51	4.12 ± 0.56	0.414 ± 0.063	3.80 ± 0.16
IV, A	77.8 ± 1.1	6.68 ± 1.20	5.91 ± 0.74	5.84 ± 0.10	0.300 ± 0.050	3.23 ± 0.17
IV, B	76.7 ± 2.7	8.11 ± 1.96	4.19 ± 1.48	7.33 ± 0.16	0.215 ± 0.058	2.32 ± 0.24
			Skeletal Muscle			
I	77.2 ± 1.9	4.06 ± 1.26	9.42 ± 2.65	2.97 ± 1.00	0.425 ± 0.063	3.72 ± 0.86
II	75.6 ± 1.9	3.89 ± 0.39	11.46 ± 1.44	2.88 ± 0.67	0.526 ± 0.084	4.20 ± 0.77
III	74.8 ± 3.4	3.56 ± 0.52	7.82 ± 1.06	3.00 ± 0.90	0.380 ± 0.030	3.53 ± 0.45
IV	73.2 ± 3.5	3.29 ± 0.79	9.76 ± 1.05	2.61 ± 0.57	0.447 ± 0.045	3.47 ± 0.80

SUMMARY

The water and electrolyte content of cardiac and skeletal muscle from patients dying of congestive failure or recent myocardial infarction was compared with the composition of specimens from patients dying of noncardiac causes. Myocardial blocks from four standard sites in the left ventricle were analyzed for water, sodium, potassium, chloride, magnesium, and phosphorus in twenty-nine cases and for water, sodium, and potassium in eighteen additional cases; blocks from the pectoralis major were analyzed for all six substances in twenty-five cases and for water, sodium, and potassium in four additional cases.

The control group comprised sixteen patients with normal hearts at autopsy and no evidence of a metabolic disorder. Myocardial analyses yielded averages of 78.8 Gm. of water, 4.96 meq. of sodium, 8.32 meq. of potassium, 4.04 meq. of chloride, 0.445 meq. of magnesium, and 3.88 meq. of phosphorus per 100 Gm. of wet tissue. Estimates of the partition of water between the extracellular and intracellular compartments and of the concentrations of base within the cells were made according to the method of Newburgh. Skeletal muscle from the same patients was comparable to myocardium in total water content, but showed a relatively smaller extracellular and larger intracellular volume. The concentration of total base in the cells was essentially the same as that in myocardium, but sodium level was slightly higher and potassium and magnesium levels were slightly lower.

Uncomplicated left ventricular hypertrophy was found in fourteen patients who showed no evidence of congestive failure during hospitalization and died of

noncardiac causes. The average content of water and each electrolyte in the myocardium was almost identical with that in the normal control group.

Congestive failure, complicating left ventricular hypertrophy, was present during hospitalization and at autopsy in eight patients. Analyses of cardiac and skeletal muscle showed significant reduction in potassium below the control values, but no significant change in content of water, sodium, chloride, magnesium, or phosphorus. The estimated partition of water in both cardiac and skeletal muscle was similar to that in the controls. The estimated intracellular concentration of total base was reduced to a similar level in cardiac and skeletal muscle, largely from potassium loss. The significance of these observations is discussed.

Recent myocardial infarction was responsible for the death of seven patients. Separate analyses were made of blocks from infarcted areas and of blocks from distant areas that appeared uninfarcted to gross examination. Infarcted myocardium showed a marked but proportionate increase in sodium and chloride, reflecting a severe interstitial edema, and an even more marked reduction in potassium, magnesium, and phosphorus, reflecting primarily losses from dead and dying cells. The analyses of distant blocks that were not grossly infarcted gave results for all five electrolytes that were intermediate between the values obtained from infarcted segments and those from normal controls. The abnormalities in chemical composition of myocardium well beyond the boundaries of a recent infarct were attributed to ischemia. Analysis of skeletal muscle from these patients did not deviate significantly from the normal.

REFERENCES

1. Iseri, L. T., Boyle, A. J., and Myers, G. B.: Water and Electrolyte Balance During Recovery From Severe Congestive Failure on a 50 Milligram Sodium Diet, Am. Heart J. **40**:706-730, 1950.
2. Boyle, A. J., Whitehead, T., Bird, E. J., Batchelor, T. M., Iseri, L. T., Jacobson, S. D., and Myers, G. B.: The Use of the Emission Spectrograph for the Quantitative Determination of Na, K, Ca, Mg, and Fe in Plasma and Urine, J. Lab. & Clin. Med. **34**:625-630, 1949.
3. Mosher, R. E., Boyle, A. J., Bird, E. J., Jacobson, S. D., Batchelor, T. M., Iseri, L. T., and Myers, G. B.: The Use of Flame Photometry for the Quantitative Determination of Sodium and Potassium in Plasma and Urine, Am. J. Clin. Path. **19**:461-470, 1949.
4. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, Cambridge, Mass., 1947, Harvard University Press.
5. Wilkins, W., and Cullen, G. E.: Electrolytes in Human Tissue. III. A Comparison of Normal Hearts With Hearts Showing Congestive Failure, J. Clin. Investigation **12**:1063-1074, 1933.
6. Mangum, G. H., and Myers, V. C.: Normal Creatine, Phosphorus, and Potassium Content of Human Cardiac and Voluntary Muscle, J. Biol. Chem. **135**:411-414, 1940.
7. Harrison, T. R., Pelcer, C., and Ewing, G.: Studies in Congestive Heart Failure. IV. Potassium Content of Skeletal and Cardiac Muscle, J. Clin. Investigation **8**:325-335, 1930.
8. Calhoun, J. A., Cullen, G. E., Clarke, G., and Harrison, T. R.: Studies in Congestive Heart Failure. VI. The Effect of Overwork and Other Factors on the Potassium Content of Cardiac Muscle, J. Clin. Investigation **9**:393-408, 1930.
9. Herrmann, G., and Decherd, G. M., Jr.: Chemical Nature of Heart Failure, Ann. Int. Med. **12**:1233-1244, 1939.
10. Scott, L. C.: The Determination of Potassium in Cardiac Muscle and the Presumable Influence of the Beta-radiations on the Rhythm, J. Clin. Investigation **10**:745-753, 1931.

11. Newburgh, L. H.: Significance of the Body Fluids in Clinical Medicine, Springfield, Ill., 1950, Charles C Thomas, Publisher.
12. Boyer, P. K., and Poindexter, C. A.: The Influence of Digitalis on the Electrolyte and Water Balance of Heart Muscle, AM. HEART J. **20**:586, 1940.
13. Mudge, G. H., and Vislocky, K.: Electrolyte Changes in Human Striated Muscle in Acidosis and Alkalosis, J. Clin. Investigation **28**:482-486, 1949.
14. Myers, V. C.: Some Chemical Changes in the Myocardium Accompanying Heart Failure, Bull. New York Acad. Med. **18**:303-317, 1942.
15. Calhoun, A. J., and Harrison, T. R.: Studies in Congestive Heart Failure: The Effect of Digitalis on the Potassium Content of the Cardiac Muscle of Dogs, J. Clin. Investigation **10**:139-144, 1931.
16. Hagen, P.: The Effects of Digilanid C in Varying Dosage Upon the Potassium and Water Content of Rabbit Heart Muscle, J. Pharmacol. & Exper. Therap. **67**:50, 1939.
17. Wedd, A. M.: The Influence of Digoxin on the Potassium Content of Heart Muscle, J. Pharmacol. & Exper. Therap. **65**:268, 1939.
18. Cattell, M., and Goodell, H.: On the Mechanism of the Action of Digitalis Glucosides on Muscle, Science **86**:106, 1937.
19. Clarke, N. E., and Mosher, R.: Electrolyte Changes in the Myocardium, reported at the Regional meeting of the American Federation for Clinical Research, Michigan, 1951; abstract, J. Michigan M. Soc. **50**:622, 1951.

VARIATION OF P-R INTERVAL IN SINUS ARRHYTHMIA AND ITS POSSIBLE RELATION TO THE WENCKEBACH PHENOMENON

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IN A number of children with rheumatic fever who showed a marked sinus arrhythmia, we observed in that part of the electrocardiogram where the heart rate was slow, that is, where the R-R interval was long, that the P-R interval was comparatively short. In that part of the electrocardiogram where the rate was fast, that is, where the R-R interval was short, the P-R interval was relatively long. For the sake of brevity this inverse relationship of the length of the P-R interval to the length of the R-R interval in some cases of sinus arrhythmia will be referred to in this paper as the P-R phenomenon. Fig. 1 shows this P-R phenomenon clearly.

Although mention of the occurrence of the P-R phenomenon is rarely encountered in medical literature, Ashman and Hull[1] made the following statement: "The P-R interval is generally practically constant; but in some sinus arrhythmias, if there is a relatively high rate during inspiration in rheumatic carditis, or after administration of digitalis, the P-R may be longer when the heart is accelerated."

We felt that a study of this phenomenon should be made especially because we thought it might be helpful in the detection of cardiac involvement in active rheumatic fever.

CLINICAL MATERIAL AND METHOD

Electrocardiograms of 107 children were taken for purposes of this study. Long strips were taken mostly of standard lead II. The electrocardiograms were studied and measured with the help of a magnifying glass which magnified fifteen times or with the help of an apparatus which is similar to a photographic enlarger where the electrocardiographic tracing was thrown on a screen many times enlarged. The latter apparatus, which served excellently for the photographic type of electrocardiograms, could not be used for the tracings with the direct-writing machine as the high temperature in the enlarger spoiled the heat-sensitive paper.

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With these techniques it was possible to estimate fairly exactly the length of the intervals in tenths of millimeters of the tracing, so that by multiplying by 0.04 the interval could be expressed in thousandths of a second.

Whenever feasible, we let the children breathe deeply in order to produce sinus arrhythmia. Since every degree of sinus arrhythmia was encountered, it was decided to use for this investigation only those strips in which the relation of the longest cycle to the shortest was at least 4 to 3. Thus, for instance, when the long cycle was 20 mm. in length and the short 15 mm., we accepted this strip, but where the relation was only 20 to 16, we called it "not enough sinus arrhythmia" and excluded it for this study.

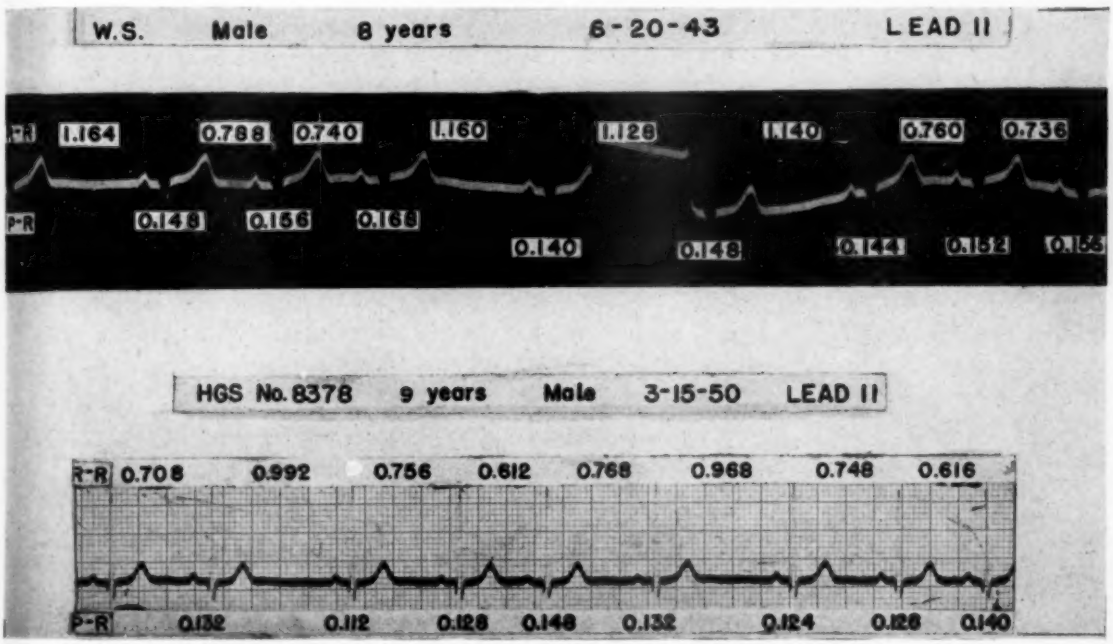

Fig. 1.—Lead II tracings of two boys with acute rheumatic fever showing sinus arrhythmia and longer P-R intervals in the shorter cycles (inverse relationship of P-R and R-R intervals).

Of the 107 children examined seventy-five showed either spontaneously or by deep breathing a sinus arrhythmia fulfilling this requirement. Of these seventy-five patients thirty-eight had rheumatic fever of various degrees of severity; eleven suffered from miscellaneous conditions, including six cases of rheumatoid arthritis and one case of sprue with accompanying electrolyte imbalance; and twenty-six children were completely normal in regard to their cardiovascular system.*

*We are grateful to Dr. Gerald N. Hoeffel and the staff of the New England Peabody Home for Crippled Children for the "normal" controls. These children suffered from various orthopedic conditions, but none had any evidence of cardiovascular disease.

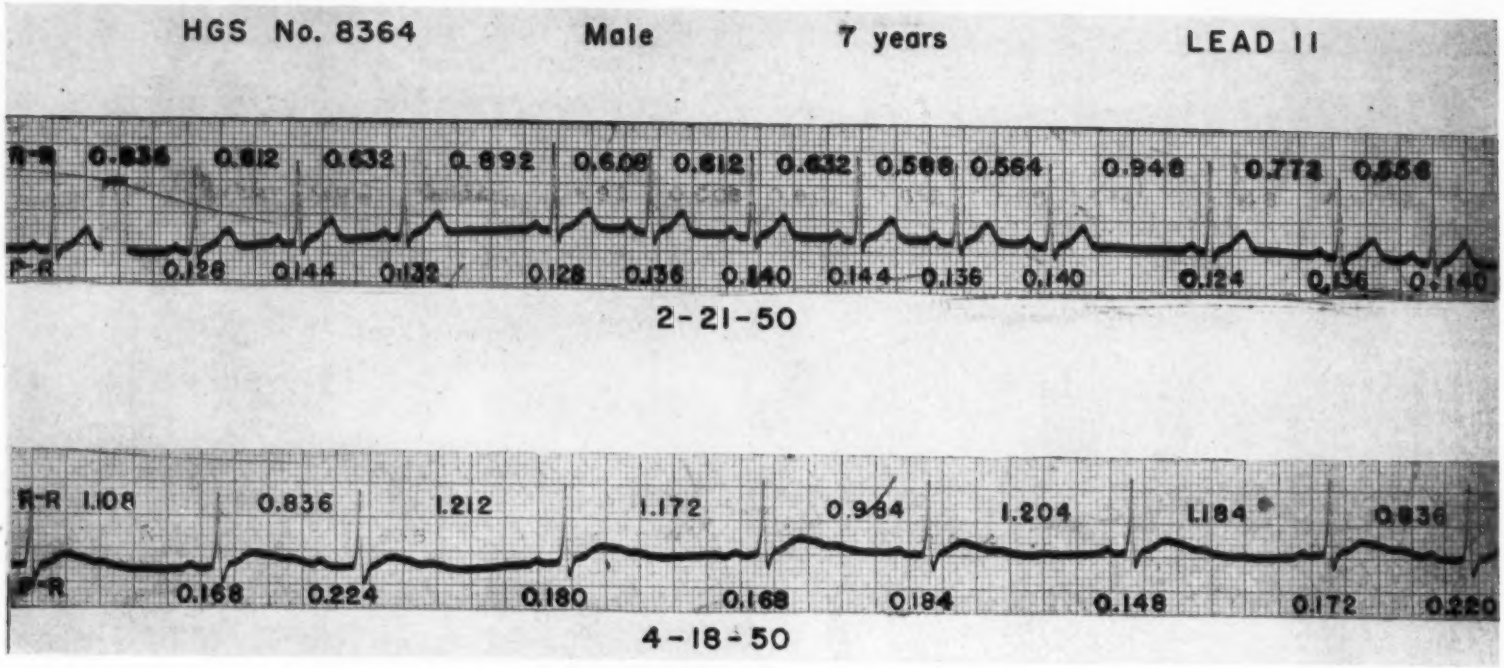

Fig. 2.—Two tracings of a boy suffering from sprue associated with marked electrolyte imbalance. The inverse relationship between P-R and R-R intervals which was already apparent in the upper tracing became much more marked as the disease progressed (lower tracing).

FREQUENCY OF THE P-R PHENOMENON IN VARIOUS CONDITIONS

Fig. 2 shows two electrocardiograms of the child with severe sprue and electrolyte imbalance. Both tracings show the P-R phenomenon. In the first one, taken on Feb. 21, 1950, the P-R interval remains within normal limits, whereas in the second tracing, taken on April 18, 1950, the P-R phenomenon is so marked that during the short cycle the P-R interval is prolonged beyond normal limits.

Fig. 3 shows an electrocardiogram of a normal child demonstrating the P-R phenomenon.

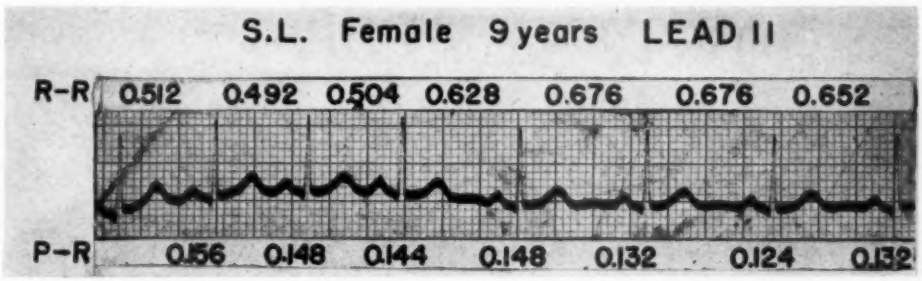

Fig. 3.—Tracing of a "normal" child showing sinus arrhythmia and inverse relationship of P-R and R-R intervals.

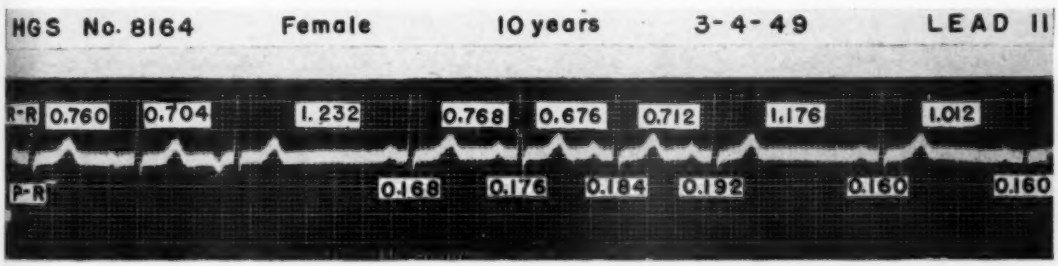

Fig. 4.—Electrocardiogram of a child with rheumatic fever. The changes in appearance of the P waves on the left side of the tracing (diphasic in the first cycle and inverted in the second) demonstrate a shift in the position of the pacemaker. Although the P waves on the right side of the tracing appear to be normal in shape, it is possible that the inverse relationship of P-R and R-R intervals in this region is being produced by a mechanism of displacement of the pacemaker without involvement of the atrioventricular node.

The frequency with which the P-R phenomenon was observed is indicated in Table I. In thirty-eight electrocardiograms of children with rheumatic fever the P-R phenomenon was definite in twenty-one instances (55 per cent). Of the eleven patients with miscellaneous diseases six showed the P-R phenomenon. Among the twenty-six normal controls eleven children (42 per cent) showed the inverse relationship of the P-R and R-R intervals.

The number of cases in these groups is not large enough to answer the question of whether the P-R phenomenon occurs more often in children with rheumatic fever than it does in children with a normal cardiovascular system. It is evident, however, that the P-R phenomenon occurs sufficiently often in normal children so that it cannot be used for a diagnosis of cardiac involvement in rheumatic fever.

TABLE I. FREQUENCY OF THE INVERSE RELATIONSHIP OF THE P-R AND R-R INTERVALS (P-R PHENOMENON) IN VARIOUS CONDITIONS

DIAGNOSES	TOTAL CASES	WITH P-R PHENOMENON	
		CASES	PER CENT
Rheumatic fever	38	21	55
Miscellaneous diseases	11	6	54
Normal	26	11	42

POSSIBLE MECHANISMS

A definite explanation for the occurrence of the P-R phenomenon cannot be given, but it is of interest to consider briefly several possible mechanisms.

1. The chronotropic inhibitory effect of the vagus may cause a *shift of the pacemaker* from the head of the sinoauricular node to the middle or the tail of this node or even to the atrioventricular node. Such an occurrence is suggested by the tracing in Fig. 4. The changes of the appearance of the P waves on the left side of the electrocardiogram (diphasic in the first cycle and inverted in the second) demonstrate a shift in the position of the pacemaker. Since the P waves on the right side of the electrocardiogram appear to be normal in shape, it is possible that the P-R phenomenon in this region is produced by a displacement of the pacemaker without, however, involvement of the atrioventricular node. The observation of Levine and co-workers[2] is consistent with this hypothesis. These investigators, by introducing an electrocardiographic electrode into the right atrium, studied the displacement of the cardiac pacemaker due to vagal stimulation. In one of their experiments in which the vagus was stimulated by right ocular pressure, they could demonstrate a dislocation of the pacemaker of about 3 cm. while the simultaneously recorded V_F tracing showed a shortening of the P-R interval from 0.14 to 0.11 second and a decrease in amplitude of the P wave.

2. It is known that vagal stimulation reduces both the amplitude and duration of the monophasic action current recorded from the auricular muscle (i.e., the size of the P wave). According to Ashman and Hull,[1] the variation in the amplitude of the P waves often observed in sinus arrhythmia is probably due to this effect more frequently than to a shift in the location of the pacemaker. Other things being equal, the P waves in sinus tachycardia are higher and sharper than in sinus bradycardia. Therefore, it is necessary to consider whether the shortening of the P-R interval may be merely a *pseudo-effect due to the impossibility of recognizing the beginning of the P waves* when their amplitude is very small. Whether such an error accounts for the P-R phenomenon can be determined by simply measuring the distance from the peak of the P wave to the peak of the R wave. Measurements of this type were made in fifteen cases and in fourteen of these the inverse relationship was still recognizable. An illustrative tracing is shown in Fig. 5. It therefore would appear that the P-R phenom-

enon is generally not due to this pseudo-effect alone, even in those instances in which the size of the P waves is markedly diminished in the long cycles.

3. Another possible explanation is that the shortening of the P-R interval is brought about by *nodal escape* occurring just before the excitation wave has reached the atrioventricular node. It is difficult to prove or disprove such a hypothesis, but it seems unlikely that this course of events would occur as often as the P-R phenomenon does.

4. The last hypothesis to be considered is that the *fibers of the conduction system*, even under normal conditions, *may conduct the impulse more slowly if they had to conduct an impulse shortly before and conduct more rapidly if they have had more time to rest.*

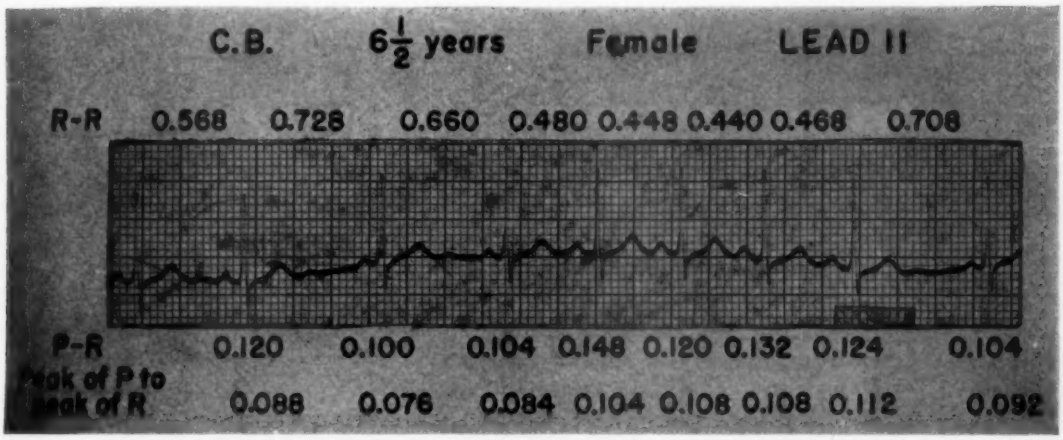

Fig. 5.—Tracing showing relationship of R-R interval to P-R interval and also to interval between peak of P and peak of R waves.

The fact that the P-R phenomenon is not observed in all instances of sinus arrhythmia may be due to the opposing dromotropic effect of the vagus, namely, the prolongation of conduction induced by vagus stimulation. The latter is generally accepted as the cause for the prolongation of the P-R interval in bradycardia.*

Ashman and Hull[1] have commented on these two opposing tendencies: "In general in a bradycardia of sinus origin the P-R interval will be slightly longer than the average, but this effect is not consistent. The reason is that the slow rate due to the inhibition gives the junctional tissue more than the normal time for recovery, and this tends to offset the inhibitory depression."

It seems to us that two of the mechanisms already considered, namely, a shift of pacemaker and a change in conduction time, may often combine to produce the P-R phenomenon. In those instances where no change in appearance of the P wave can be seen, the change in conduction time probably plays the more important role. Since the P-R phenomenon is also seen quite often in normal

*Schlamowitz[2] has some doubt about the statistical significance of the positive correlation of the lengths of the P-R and R-R intervals.

persons without change in appearance of the P waves, it appears that even in normal hearts the conducting tissue conducts more quickly if it has had longer time to recover and conducts more slowly if it has had a shorter time to recover.

POSSIBLE RELATIONSHIP OF P-R PHENOMENON AND WENCKEBACH PHENOMENON

In the Wenckebach phenomenon we see how even in a regular sinus rhythm the pathologically exaggerated fatigability of the conducting tissue produces from cycle to cycle slower and slower conduction and thus longer and longer P-R intervals until a complete block is reached. Then the tissue has time to recover, the P-R interval becomes short again, and the same course of events is repeated.

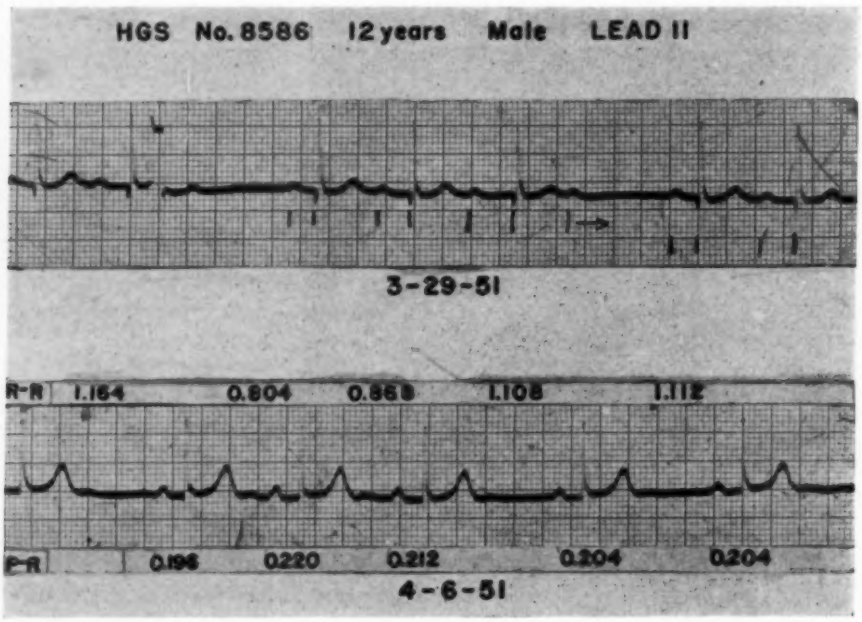

Fig. 6.—Two electrocardiograms of a child with rheumatic fever. The upper tracing shows the typical Wenckebach phenomenon, while the lower tracing taken one week later shows the inverse relationship of P-R and R-R intervals (P-R phenomenon).

In the P-R phenomenon, which can be recognized only in patients with sinus arrhythmia, the better recovery of the conducting tissue, when the cycle is long, is shown by a short P-R interval, whereas the normal fatigue, when the cycle is short, is shown by a longer P-R interval. In contrast to the Wenckebach phenomenon, in the P-R phenomenon the disturbance in conduction is not of sufficient magnitude to result in dropped beats. Since the correlation between fatigue of the conducting tissue and lengthening of the P-R interval is the generally accepted explanation for the Wenckebach phenomenon, *it would appear that the Wenckebach phenomenon is caused by a pathologic exaggeration of a characteristic of the conducting tissue frequently found under normal conditions.* That this interpretation may possibly be correct is suggested by the case illustrated in Fig. 6, which shows two electrocardiograms of a child with rheumatic fever.

The upper tracing reveals the typical Wenckebach phenomenon, while the lower tracing taken one week later shows the P-R phenomenon.

SUMMARY

1. The P-R interval often shows an inverse relationship to the R-R interval in sinus arrhythmia.

2. When this phenomenon was first observed, it was thought possibly to be specific for active rheumatic fever. Further study, however, showed that it occurred in many individuals with normal hearts.

3. Four possible explanations for this P-R phenomenon are discussed.

4. It is suggested that the Wenckebach phenomenon may be due to a pathologic exaggeration of the fatigability of the conducting tissue frequently found even under normal conditions.

We wish to express our appreciation to Dr. Louis Wolff, Dr. Conger Williams, and Dr. Arthur Linenthal for their interest and helpful suggestions.

REFERENCES

1. Ashman, Richard, and Hull, Edgar: The Essentials of Electrocardiography, ed. 2, New York, 1941, The Macmillan Company.
2. Levine, Harold D., Hellems, Harper K., Dow, James W., and Gowdey, John: Studies in Intracardiac Electrocardiography in Man. III. Displacement of the Cardiac Pacemaker, Am. J. Physiol. **156**:19, 1949.
3. Schlamowitz, Isadore: An Analysis of the Time Relationship Within the Cardiac Cycle in the Electrocardiograms of Normal Men. III. The Duration of the P-R Interval and Its Relationship to the Cycle Length (R-R Interval), AM. HEART J. **31**:473, 1946.

POSITIONAL CHANGES IN Q_{AVF} AND THE ESOPHAGEAL LEADS INDUCED BY PNEUMOPERITONEUM

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IN RECENT years, it has become increasingly apparent that the diagnosis of posterior wall myocardial infarction is largely based on the presence of a significant Q wave in standard leads and the unipolar left leg lead (aV_F). The aV_F lead is considered more significant because of the lack of specificity for posterior myocardial infarction of a deep Q_3. Its importance has been affected as yet only slightly by the increasing, although still limited, use of the esophageal lead in clinical electrocardiography.[1,2,3,4,6,8]

Various criteria have been offered to establish the significance of a Q_{AVF}.[1,2,4,5,7,8,9] These have been partially summarized by Yu and Blake[10] who classified the criteria for a significant Q_{AVF} into two groups: "(1) A Q wave in the left leg lead has a voltage of 40 per cent or more of the entire QRS complex in the same lead, has a duration of 0.04 second or more, and is associated with an inverted T wave; (2) a Q wave in the left leg lead has a voltage of 25 per cent or more of the R wave in the same lead, and has a duration of 0.04 or more second." Criteria such as these have been considered by some to apply only when the total QRS voltage in aV_F exceeds 0.7 mv.[7,8] The degree of accuracy of the Q_{AVF} diagnosis of posterior myocardial infarction is of some question.[1,6,10] Not only may infarction cause a deep Q_{AVF}, but positional changes may do it as well.[6,11]

In esophageal leads significant Q waves are normally present in supra-auricular, auricular, and transition zones. Significant Q waves in the ventricular zone, however, are thought to indicate underlying infarcted muscle.[1,4] The ventricular zone may be considered to start at least 5 cm. below the site of the lowest intrinsic P wave.[3,4] Recent studies indicate that a point at least 7.5 cm. below the level of the lowest intrinsic P wave might be a more definite boundary for the start of the ventricular zone.[5] Careful consideration of this feature may serve to lessen the danger of confusion of the levels of appearance of ventricular cavity and surface potentials in relation to the intrinsic auricular deflection and to obviate the need for simultaneous recording of three or more different electrocardiographic leads, as recently suggested.[12]

Scherlis and associates[12] have recently stated that significant Q waves in the esophageal ventricular leads may also be found in ventricular hypertrophy. Evans and Black[13] have described abnormal esophageal Q waves at levels they consider ventricular, as a result of pneumoperitoneum, with or without phrenemphraxis. Our study was designed to re-evaluate the effect of pneumoperitoneum

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on the esophageal leads and aV_F. The technique used was pneumoperitoneum without phrenemphraxis but with postural and respiratory changes. The patients were also studied with as much air removed as feasible to define more clearly the effects of pneumoperitoneum on the electrocardiogram.

METHODS

Twelve tuberculous patients under pneumoperitoneum therapy without phrenemphraxis received electrocardiographic studies. All were in a moderately to far-advanced stage of tuberculous pulmonary disease. None had evidence of heart disease by history, physical examination, or roentgenographic study. One patient (M. L.) displayed a right bundle branch block in the electrocardiogram. The patients ranged from 20 to 60 years of age, but eight were under 45 years. They included ten men and two women; five were asthenic, five were sthenic, and two were hypersthenic.

The standard limb leads, augmented unipolar limb leads,[14] at least six unipolar precordial leads (Wilson technique), and a full series of esophageal leads at intervals of 2.5 to 5 cm. were taken with the patient in the sitting position as a control. Respiratory variations were noted in both the aV and esophageal leads. Then, from 1,200 to 2,500 ml. of air were withdrawn from the peritoneal cavity, and the entire electrocardiographic survey was repeated in both the supine and sitting positions. At this point, all of the air removed from the peritoneal cavity was replaced, and from 1,000 to 2,000 ml. of additional air were then injected into the patient until he reported a subjective sensation of abdominal fullness or tightness. This last procedure will henceforth be termed "augmented air refill." Electrocardiographic studies were then repeated, in both the supine and sitting positions. For the purposes of simplicity, only the results with the patient supine and the air out and sitting with augmented air refill will be presented; these demonstrated the most marked changes.

The evacuation and replacement of air ensured a wide range of intra-abdominal pressures, a total exchange of 2,200 to 4,000 ml. of air resulting. Intraperitoneal pressures, taken with a Zavod pneumoperitoneum apparatus, averaged plus 6, plus 8 at the beginning of the procedure, fell to plus 2, plus 4, and then rose to plus 12, plus 16 at the end of the study. A Sanborn Viso-Cardiette was used for most of the tracings; a Cambridge Simpli-Trol model was used in a few cases.

RESULTS

Eleven of the twelve patients studied had no significant Q waves in aV_F when they were in the supine position with air removed (Table 1). One of these patients (M. L., Fig. 1) developed a significant Q_{AVF} in the sitting position after augmented air refill; this patient has a constant right bundle branch block pattern. Three other patients (M. S., E. R., and J. G., Figs. 2, 3, and 4, respectively) developed a significant Q_{AVF} in the sitting position after augmented air refill, but only with expiration. One patient (R. W.) displayed a significant Q wave with air out and in the supine position; paradoxically, this Q wave diminished in size with augmented air refill and the sitting position.

TABLE I.

PATIENT	DEEP Q_{AVF}*		LOWEST LEVEL OF DEEP Q_E		LOWEST INTRINSIC P		SIGNIFICANT Q_3†		PRECORDIAL LEADS§		DECREASE IN T_2§	INCREASE IN R_{AVL}§	LEFT AXIS DEVIATION§
	OSu	ISi	OSu	ISi	OSu	ISi	OSu	ISi	ROTATION‡	DECREASE IN T WAVES			
J. D.	—	—	50	52	50	57	—	—	—	+	+	+	+
J. G.	—	1.5/4 (E)	45	70	45	50	—	—	C	—	+	+	+
M. L.	—	2.5/8	50	60	60	60	—	3/11	C	—	+	+	+
E. M.	—	—	35	60	40	60	—	3/5	CC	—	+	+	+
M. P.	—	—	50	50	40	55	—	—	—	—	—	+	+
E. R.	—	2/3.5 (E)	45	70	45	50	3/10	—	C	—	+	+	+
M. S.	—	3/5 (E)	40	70	40	55	—	—	C	—	+	+	+
H. S.	—	—	50	45	50	55	—	—	C	—	+	+	+
E. S.	—	—	50	55	50	55	—	—	CC	—	+	+	+
R. T.	—	—	40	55	40	45	—	—	C	—	+	—	—
A. v.B.	—	—	35	70	40	50	—	7/1	C	+	+	+	+
R. W.	2/7	—	55	50	50	55	2.5/7	4.5/9	C	—	+	+	+

Note: The fractions depicted above represent the Q/R ratio.
*OSu = air out, supine
ISi = augmented air refill, sitting
(E) = expiration
†Relation of Q with the highest R in the standard leads.
‡C = clockwise
CC = counterclockwise
§In ISi position.

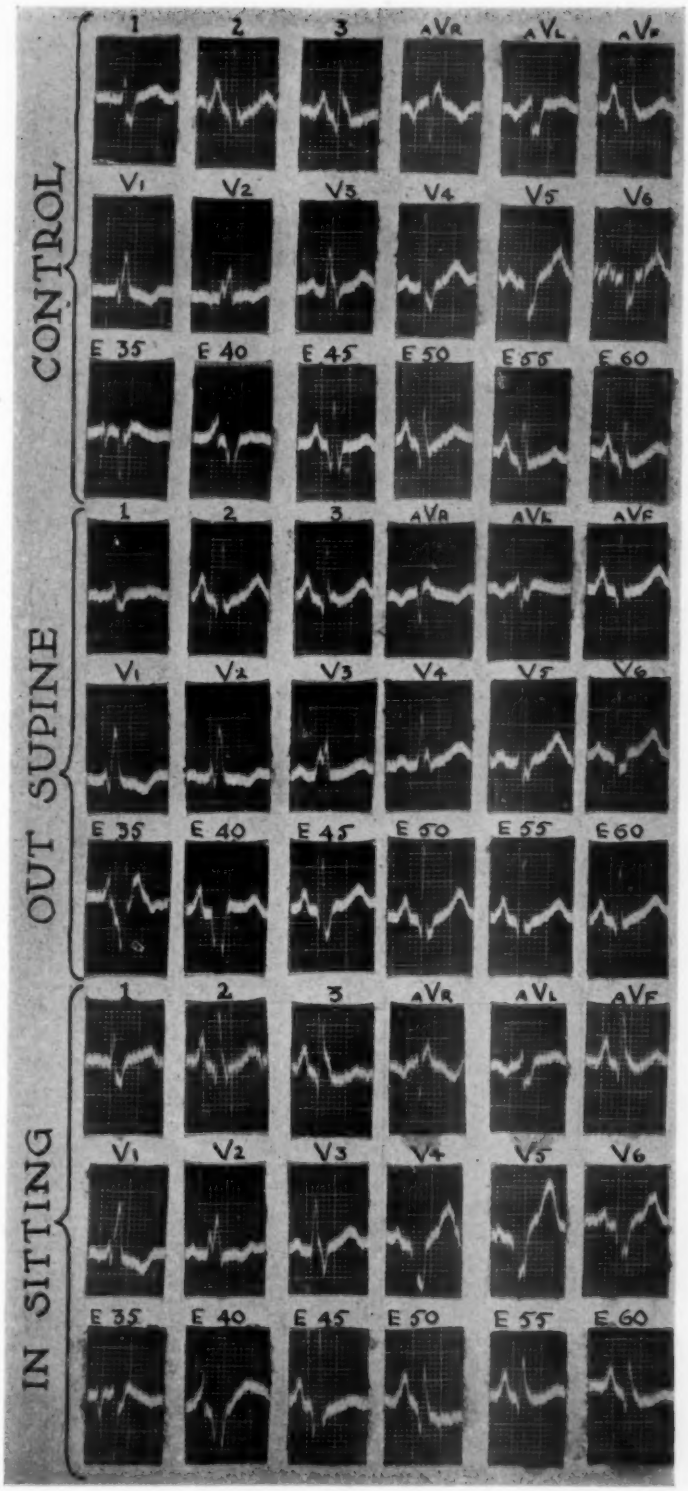

Fig. 1.—M. L., a 60-year-old, asthenic, white man, with bilateral pulmonary fibrosis, emphysema, and tuberculosis. Control pressures equal plus 6, plus 10; after removal of 1,500 c.c. of air, plus 2, plus 4; after augmented air refill of 3,000 c.c., plus 10, plus 16. Note the presence of the right bundle branch block pattern. There are deep Q waves in aV_F and in the esophageal leads at lowest levels in the in sitting position with normal Q waves in the out supine and control tracings.

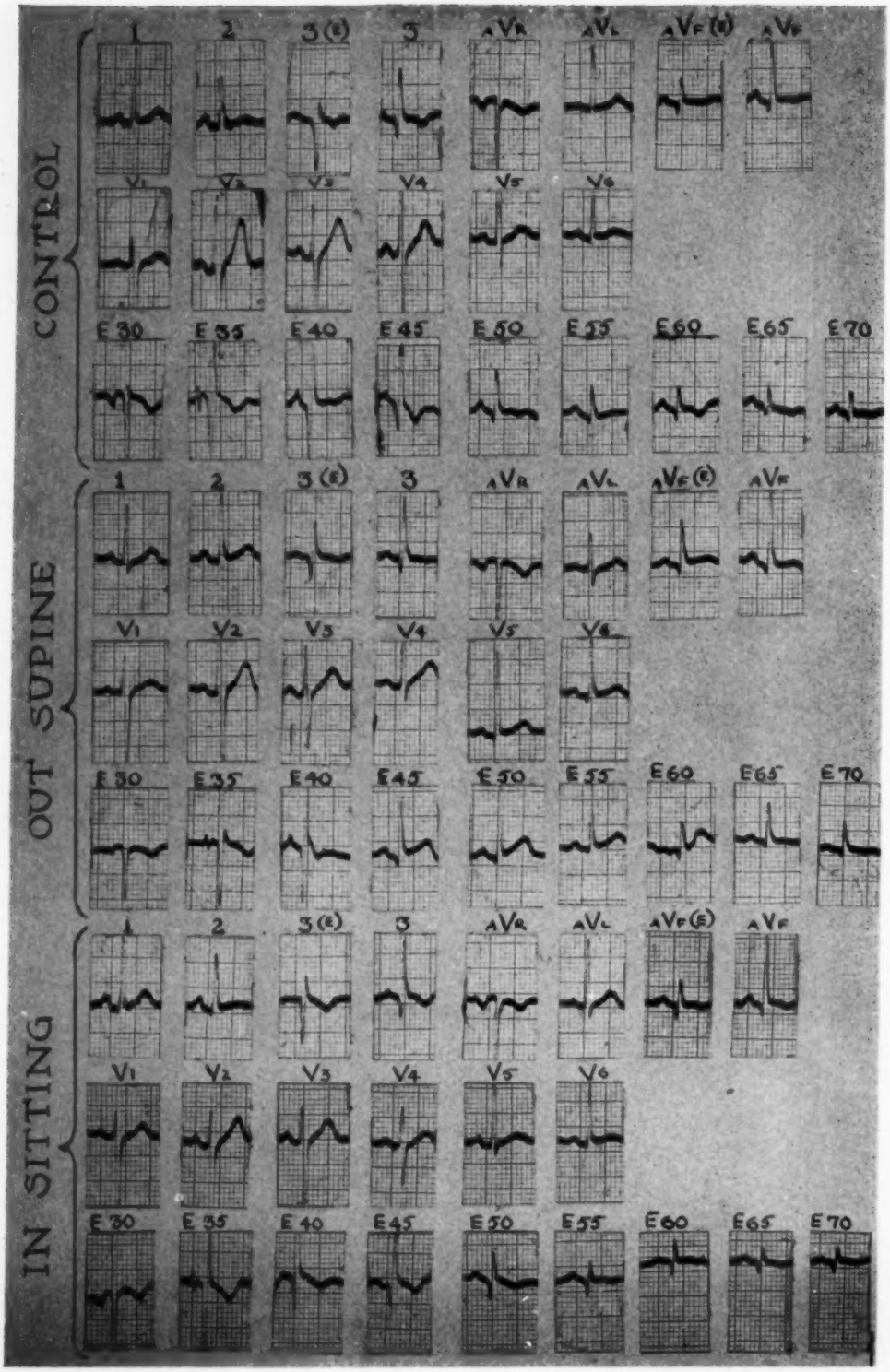

Fig. 2.—M. S., a 32-year-old asthenic, white man, with bilateral fibrocaseocavernous pulmonary tuberculosis. Control pressures equal plus 4, plus 8; after removal of 1,500 c.c. of air, plus 2, plus 4; after augmented air refill of 3,000 c.c., plus 12, plus 16. Note the presence of deep Q waves in aV_F with expiration [$aV_F(E)$] and in esophageal leads at lowest levels in the in sitting position with normal Q waves in these leads in the out supine position.

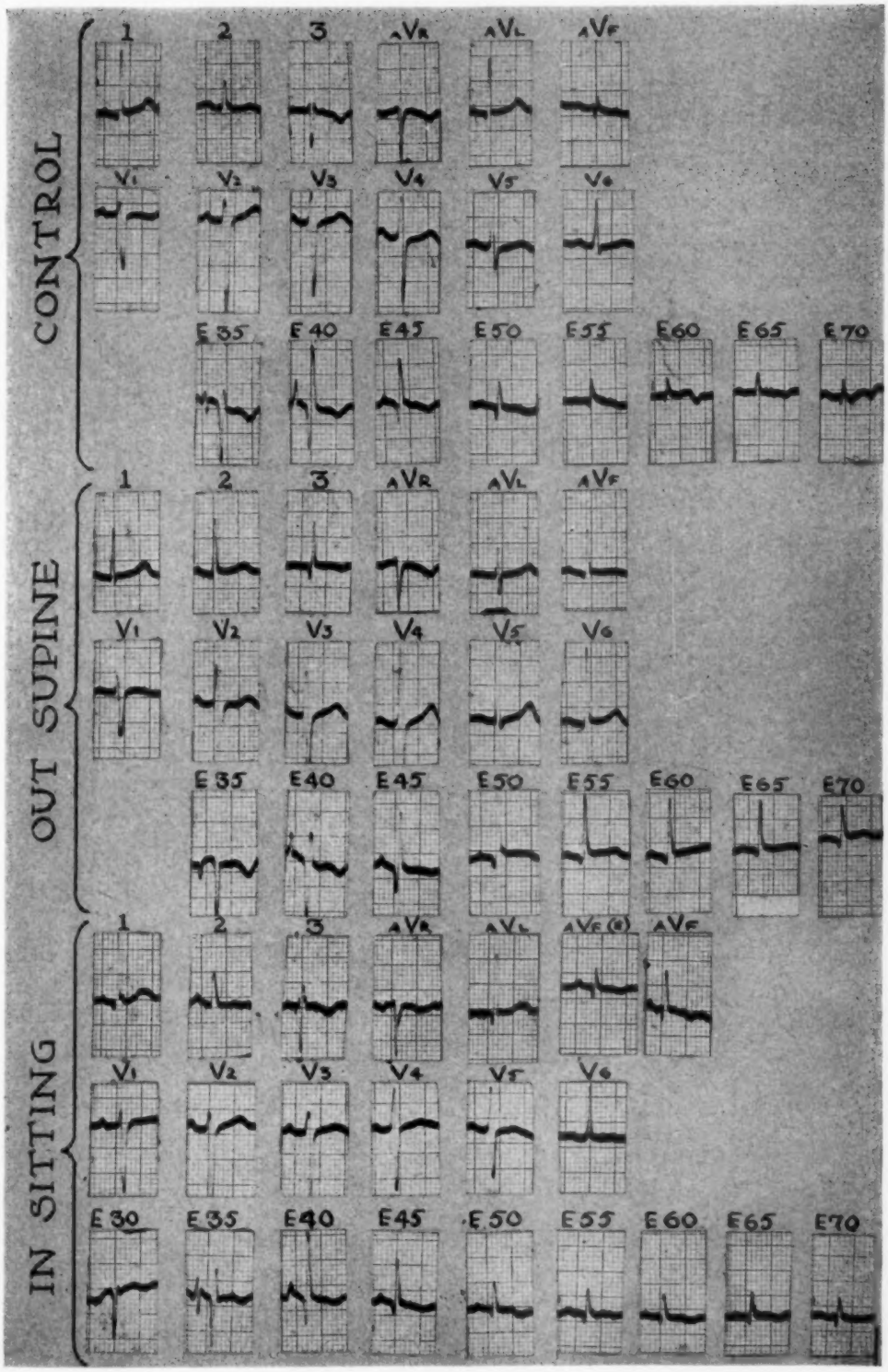

Fig. 3.—E. R., a 27-year-old, asthenic, white man, with bilateral fibrocaseocavernous tuberculosis. Control pressures equal plus 8, plus 12; after removal of 1,500 c.c. of air, plus 2, plus 6; after augmented air refill of 3,000 c.c., plus 12, plus 16. Note the presence of the deep Q in aV_F with expiration [$aV_F(E)$] and in esophageal leads at lowest levels in the in sitting position with normal Q waves in these leads in the out supine position.

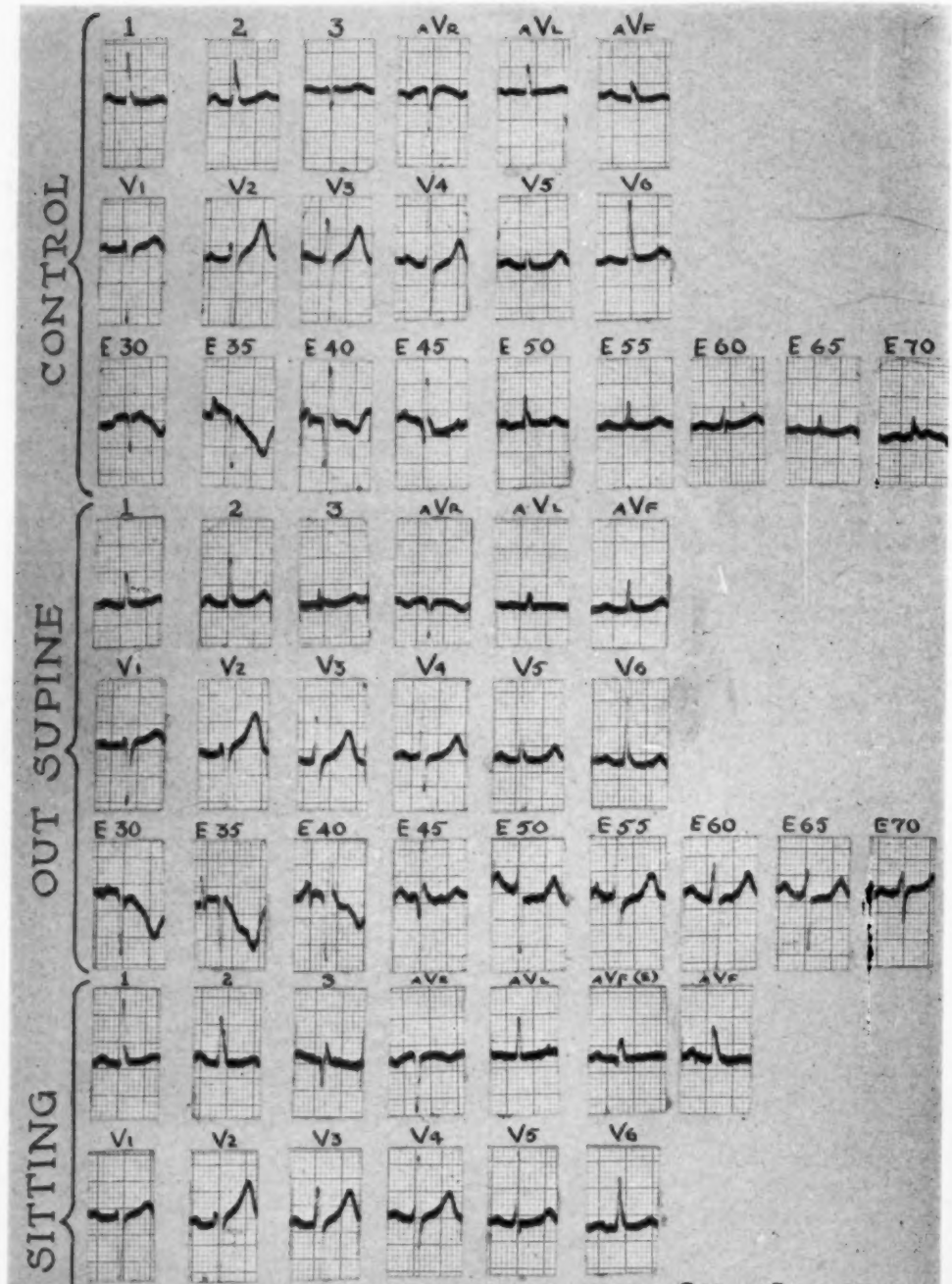

Fig. 4.—J. G., a 55-year-old, hypersthenic white man, with bilateral fibrocaseocavernous pulmonary tuberculosis. Control pressures equal plus 4, plus 6; after removal of 1,000 c.c. of air, plus 3, plus 5; after augmented air refill of 3,000 c.c., plus 12, plus 16. Note the presence of a deep Q wave in aV_F with expiration [$aV_F(E)$] and in esophageal leads at lowest levels in the in sitting position and absence of Q waves in the out supine position.

No patient studied showed a significant Q wave at ventricular levels in the esophageal lead when supine with air removed. Seven patients developed deep Q waves in the esophageal leads, at levels generally considered ventricular, in the sitting position after augmented air refill, four down as far as 70 cm. from the nares, two down as far as 60 cm., and one at 55 cm. (Table I). Lower levels were noted in expiration than in inspiration. One other patient (E. S.) developed borderline Q waves at these levels in the sitting position after augmented air refill. In all these patients, there was marked lowering of the QRS voltage at the distal levels where deep Q waves were present. In all but one of these patients there was a lowering of the level of the most inferior intrinsic-type (peaked) P wave. Between the supine position with air removed and the sitting position with augmented air refill, there was a lowering of the intrinsic P wave between 5 and 20 cm. This effect could be accentuated by expiration.

All four patients who developed a significant Q_{AVF} in the sitting position after augmented air refill also had deep Q waves present at lower esophageal levels, but three patients who developed these Q waves in the lower esophageal leads did not develop a significant Q_{AVF} (Table I).

Two patients (R. W. and E. R.) demonstrated an abnormal Q_3[15] when supine with air out, one of whom (R. W.) also had a significant Q_{AVF} at that time. Four patients developed abnormal Q_3 in the sitting position after augmented air refill, of whom only one had a significant Q_{AVF} (M. L.), but three of these patients showed a lowering of the level of the deep Q waves found in the esophageal leads (Table I).

After augmented air refill in the sitting position, several other changes were noted (Table I). Examination of the precordial leads revealed clockwise rotation in eight patients, counterclockwise rotation in two, and no change in two. In two cases, T waves in the precordial leads became lower to inverted. In the standard limb leads, tendency to left axis deviation was noted in eleven patients. These patients also developed concomitant increase in the amplitude of R_{AVL}. A decrease in amplitude of T_2 was noted in eleven of the patients.

DISCUSSION

It has been postulated[6,11] that occasionally deep Q waves in aV_F may represent the transmission of the electrical potential of the posterior basal surface of the heart toward the left leg electrode. The mechanism for this has been considered to be the rotation of the heart on its transverse axis.[13] This rotation would cause an elevation of the anterior portion of the heart, with a corresponding lowering of the posterior aspect of the heart. These changes would cause the esophageal lead transition zone to migrate downward toward the stomach. This might be reflected, in a certain number of patients, by deep Q waves in aV_F. Expiration, which further elevates the diaphragm, would tend to accentuate the abnormality. With the patient supine and air removed, the diaphragm would become lower, and the entire pattern of esophageal and aV_F leads would then tend toward normal. Our technique was designed to test this mechanism.

From our results, it is apparent that deep Q waves can appear in aV_F in patients without heart disease. In one patient, a significant Q_{AVF} was developed

in the sitting position when the abdomen was overdistended; three other patients demonstrated this only upon expiration under the same circumstances. All these patients developed changes in the esophageal leads. These consisted of a lowering of the electrical patterns of the auricular and transitional levels below the diaphragm; thus, Q waves would appear as far down as esophageal levels could be recorded. Three other patients developed similar changes in the esophageal lead without corresponding changes in aV_F.

None of these patients had clinical evidence of heart disease, and these changes were reversible in all. It is felt, therefore, that in the patients studied these deep Q waves in aV_F and in the lower esophagus and upper stomach were not indicative of heart disease. The deep Q waves in the lower esophageal leads were due to a lowering of the entire auricular and transitional zones of the heart (the so-called posterior basal surface). This shift of the posterior basal surface, where deep Q waves are normally present, was also the apparent cause of the deep Q waves in aV_F. It was noted that the total QRS voltage in the lower esophageal leads was decreased in all these patients in the sitting position with augmented air refill. The reason for this is uncertain, but the forward rotation of the heart may widen the gap between it and the lower esophagus.

In three patients with augmented air refill, the lowest esophageal intrinsic P wave did not correspond to within 20 cm. of the lowest Q wave. Since these deep Q waves at lower esophageal levels did not represent ventricular infarction one must assume that the Q waves are positional in origin and are representative of the transitional zone. It would appear, therefore, that the transitional zone between the auricular and ventricular levels, as determined by the intrinsic P wave, can be greater than 5 to 7.5 cm. and may be as great as 15 to 20 cm. This may only be found with abnormal elevation of the diaphragm.

Any condition which will markedly elevate the diaphragm may cause difficulty in interpreting both the esophageal lead and aV_F. The most important factor in judging the esophageal lead, therefore, is not the distance between the level of the electrode and the nares, but its relation to the intrinsic P wave. The limitations of the use of the intrinsic P wave are discussed. The differentiation of a deep Q_{AVF} is more difficult. Goldberger[16] mentioned that with an abnormal Q_{AVF}, Lead aV_R shows an rS or QS pattern and that association of a QR, Qr, or qR pattern in aV_R renders a QR pattern in aV_F normal, unless anterior infarction is also present. In all of our cases, only rS or QS patterns were present in aV_R; therefore, this criterion did not prove valid in our cases. Study was also made of the relationship of a deep Q_3 to similar waves in aV_F and the esophageal lead. In general, there was less correlation between Q_3 and the esophageal lead than between Q_{AVF} and the esophageal lead.

Admittedly, the degree of abdominal distention herewith obtained is greater than one sees in most cases. However, in patients with pneumoperitoneum, ascites, hepatomegaly, marked obesity, pregnancy, gastric dilatation, and tympanitis, these positional changes should be considered.

SUMMARY

1. With marked elevation of the diaphragm, as in pneumoperitoneum, deep but reversible Q waves may appear in aV_F in patients without heart disease.

2. Concomitant changes are seen in the esophageal leads; there is a marked lowering of the auricular and transitional zones to levels usually considered ventricular. The Q waves normally present at the auricular and transitional levels are thereby oriented toward the left leg, resulting in a deep Q_{AVF}.

We wish to thank Dr. Sidney Rothbard, Chief of the Division of Pulmonary Diseases, Montefiore Hospital, for his cooperation in the selection of the patients and Dr. S. P. Schwartz, Attending Physician, Division of Medicine, Montefiore Hospital, for his helpful criticism and advice.

REFERENCES

1. Myers, G. B., and Oren, B. G.: The Use of the Augmented Unipolar Left Leg Lead, in the Differentiation of the Normal From Abnormal Q Wave in Standard Lead III, AM. HEART J. **29**:708, 1945.
2. Myers, G. B., Klein, H. A., and Hiratzka, T.: Correlation of Electrocardiographic and Pathologic Findings in Posterior Infarction, AM. HEART J. **38**:547, 1949.
3. Hamilton, J. G. M., and Nyboer, J.: The Ventricular Deflections in Myocardial Infarction; An Electrocardiographic Study Using Esophageal and Precordial Leads, AM. HEART J. **15**:414, 1938.
4. Nyboer, J.: Exploratory Electrocardiograms (Extremity, Precordial, Esophageal) and Discussion of the Q_3 Electrocardiogram, Tr. A. Life Insur. M. Dir. America **30**:31, 1947.
5. Kistin, A. D., Brill, W. D., and Robb, G. P.: Normal Esophageal and Gastric Electrocardiograms; Descriptions, Statistical Analysis, and Bearing on Theories of "Electrocardiographic Position," Circulation **2**:578, 1950.
6. Rubin, I. L., and Rose, O. A.: The Correlation Between the Q Waves of aV_F and Esophageal Leads in the Diagnosis of Posterior Myocardial Infarction, Ann. Int. Med. **34**:632, 1951.
7. Sokolow, M., and Friedlander, R. D.: The Normal Unipolar Precordial and Limb Lead Electrocardiogram, AM. HEART J. **38**:665, 1941.
8. Sokolow, M.: The Clinical Value of Unipolar Extremity (aV) Leads, Ann. Int. Med. **34**:921, 1951.
9. Goldberger, E.: The Differentiation of Normal From Abnormal Q Waves, AM. HEART J. **30**:341, 1945.
10. Yu, P. K. G., and Blake, T. M.: The Significance of Q_{AVF} in the Diagnosis of Posterior Infarction, AM. HEART J. **40**:545, 1950.
11. Myers, G. B., and Klein, H. Q.: The Relation of the Unipolar Limb Leads to Precordial and Esophageal Leads, AM. HEART J. **35**:727, 1948.
12. Scherlis, L., Wener, J., Grishman, A., and Sandberg, A. A.: The Ventricular Complex in Esophageal Electrocardiography, AM. HEART J. **41**:246, 1951.
13. Evans, E., and Black, T. C.: The Electrocardiogram in Pneumoperitoneum: Including Augmented Unipolar Limb Leads and Unipolar Chest and Esophageal Leads, Am. Rev. Tuberc. **61**:335, 1950.
14. Goldberger, E.: A Simple, Indifferent Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented Unipolar Extremity Leads, AM. HEART J. **23**:483, 1942.
15. Pardee, H. E. B.: Significance of Electrocardiograms With Large Q in Lead III, Arch. Int. Med. **46**:470, 1930.
16. Goldberger, E.: Unipolar Lead Electrocardiography, ed. 2, Philadelphia, 1949, Lea & Febiger, p. 208.

INTRAVENTRICULAR PRESSURE AND ELECTROCARDIOGRAPHIC RECORDINGS OF THE DYING RABBIT HEART

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SINCE Rhomer's[1] original work, frequent reports have been made on electrocardiographic observations during death. Turner[2] presented a review of the electrocardiographic changes during death in seventy cases in which the most frequent findings were slowing of the rate and the appearance of an atrioventricular, nodal, or idioventricular rhythm. Hanson, Purks, and Anderson[3] reported similar changes during and after death in twenty-five cases and stated that a slow nodal rhythm occasionally occurred after the patient was clinically dead. Grieco and Schwartz[4] reported a case of a patient with acute coronary thrombosis in whom electrocardiographic activity continued for twenty-eight minutes after the patient appeared to be dead. Goodrich and Needles[5] and Krell[6] have reported similar cases in which no evidence of life existed except that in the electrocardiogram.

This study was designed to record the intracardiac pressure and the electrocardiogram in order to observe simultaneously electrical and muscular activity in the dying animal.

METHODS

Intracardiac pressures and standard Lead II electrocardiograms were simultaneously recorded on a constant speed kymograph on ten rabbits (Group I) lightly anesthetized by intravenous pentobarbital sodium. Blood pressures within the right ventricle were obtained with a No. 6 ureteral catheter introduced through the exposed right jugular vein and attached to a Statham P23A pressure transducer coupled to a 60 cycle carrier system and a high-gain stabilized amplifier which drove an Esterline-Angus 1 Ma. recorder. The transducer system was calibrated against a mercury manometer. Heparinized saline solution was used to fill the transducer and catheter system. Fatal anaphylaxis was produced by the sudden intravenous administration of 500 mg. of bovine gamma globulin (fraction II, Armour) in 10 ml. of physiological saline in five sensitized animals after the technique of Bukantz, Johnson, and Alexander.[7] Similarly five animals were given 1.5 mg. per kilogram of body weight of histamine base as a rapid lethal dose. In each experiment the catheter position was checked at autopsy and carefully examined for patency.

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In a second group of eight rabbits weighing 4.0 to 5.0 kg. right intraventricular pressures and Lead II electrocardiograms were recorded while the heart was directly observed through a right anterior thoracotomy. In two animals ventricular contractions were recorded on a revolving smoked drum via a lever system from a small tissue hook attached to the epicardium. Catheter position was determined by palpation through the chest opening, and contractions could be observed in both auricles and the right and portions of the left ventricle. Death was produced either by exsanguination or the administration of lethal intravenous doses of pentobarbital sodium.

RESULTS

In the first group of animals death came rapidly after the injection of the globulin or histamine and was marked by cessation of respiration and a transitory rise in right ventricular pressure which gradually decreased in amplitude until no ventricular pulsatile changes could be demonstrated. Prior to the disappearance of pulsatile changes the animals appeared to be clinically dead, i.e., respiration and heart beat were absent and no eye reflex could be elicited. Table I summarizes the results obtained in this group of animals. In each animal electrocardiographic activity was present after clinical death and after pulsatile recordings from the ventricle had ceased.

Persistence of electrocardiographic activity after cessation of intracardiac pressure changes varied from one to twelve minutes. The electrocardiographic changes after clinical death were not constant: tachycardia or bradycardia often appeared early with ventricular irregularity, idioventricular rhythm, ventricular fibrillation, and block occurring later.

Table II presents the results obtained in the second group of animals. Electrocardiographic activity was present as long as twenty-three minutes after cessation of pressure changes and for as long as eighteen minutes after myocardial contractions could no longer be observed. For varying periods of time after cessation of pulsatile changes minute superficial muscular undulations which finally stopped could be correlated with the electrocardiographic record. In animal E, after the electrocardiogram lost its ventricular complex, persistent P waves were associated with a small focal movement in the right auricle. In this series, as in Group I, each animal appeared clinically dead before pressure recordings ceased.

The progressive development of various arrhythmias in the absence of pulsatile activity is demonstrated in Figs. 1 and 2. The final recording (Fig. 1) appears as definite ventricular fibrillation.

DISCUSSION

Origin of electrical changes during death could be from either the myoneural conduction system or from the heart muscle itself. It has been demonstrated[8] that injured nerve tissue produces an altered electrical state and partial depolarization of the cell membranes with a resultant hyperexcitability. Ischemic heart

TABLE I. OBSERVATIONS ON THE DYING RABBIT HEART

RABBIT NO.	CONTROL HEART RATE (PER MINUTE)	CONTROL RIGHT INTRAVENTRICULAR PRESSURE (MM. Hg.)		DURATION OF ECG AFTER ABSENCE OF PULSATILE CHANGE (MINUTES)	FINAL HEART RATE (PER MINUTE)	IMMEDIATE ECG CHANGE	LATE ECG CHANGE	REMARKS
		SYSTOLIC	DIASTOLIC					
1	200	10	4.5	1.0	100	Ventricular tachycardia	Idioventricular rhythm	Questionable persistence of electrical activity
2	240	8	3.3	3.0	90	Sinus mechanism; ventricular premature beats	Irregular ventricular complexes	3 second periods of arrest
3	240	8	2.2	2.0	60	Sinus bradycardia	Idioventricular rhythm; rare P wave	Questionable persistence
4	210	11	3.3	6.0		Sinus bradycardia	Ventricular fibrillation	Intermediate period of minute complexes
5	180	6	2.8	12.0	60	Sinus tachycardia, then ventricular tachycardia	2:1 A-V block; idioventricular rhythm	2 minutes of apparent electrical inactivity
		AMPLITUDE OF PULSATION (CM.)						
6	240	1.3		1.5	180	Sinus bradycardia	Ventricular tachycardia	Questionable persistence
7	180	0.5		1.5	60	Sinus bradycardia	Sinus bradycardia	Questionable persistence
8	240	0.7		2.0		Tachycardia	Ventricular fibrillation	Questionable persistence
9	210	0.9		3.0	120	Ventricular tachycardia	2:1 block	Bizarre complexes
10	240	0.7		4.0	270	Auricular tachycardia (small complex)	Ventricular tachycardia (large complexes)	

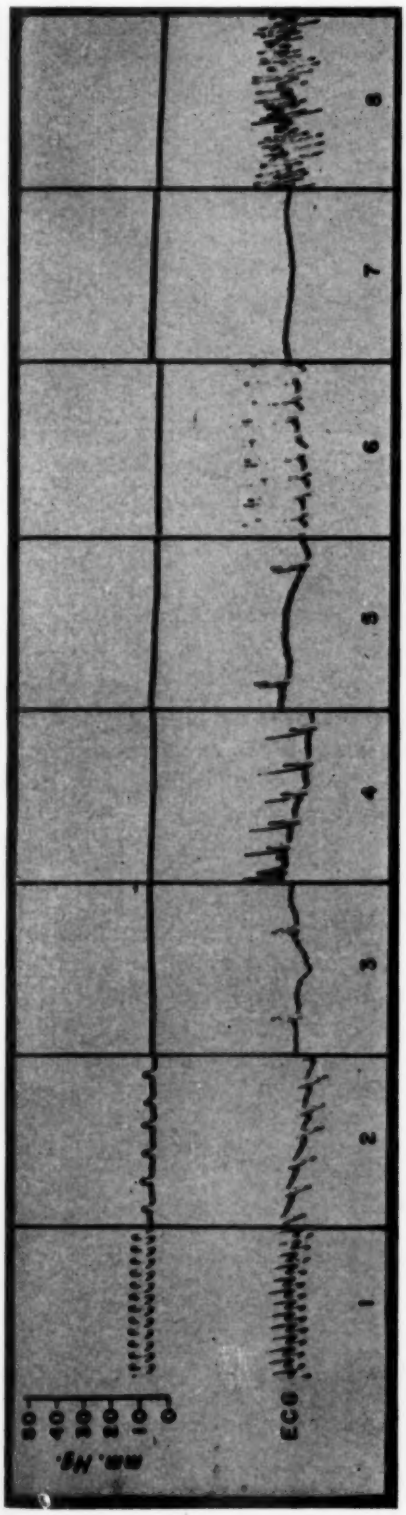

Fig. 1.—Serial intracardiac pressure and electrocardiographic recordings of the dying rabbit heart, animal No. 4. *1*, Previous to death; *2*, at death; *3*, 1.5 minutes; *4*, 2.5 minutes; *5*, 3.0 minutes; *6*, 4.0 minutes; *7*, 4.5 minutes; *8*, 5.5 minutes after cessation of pulsatile changes.

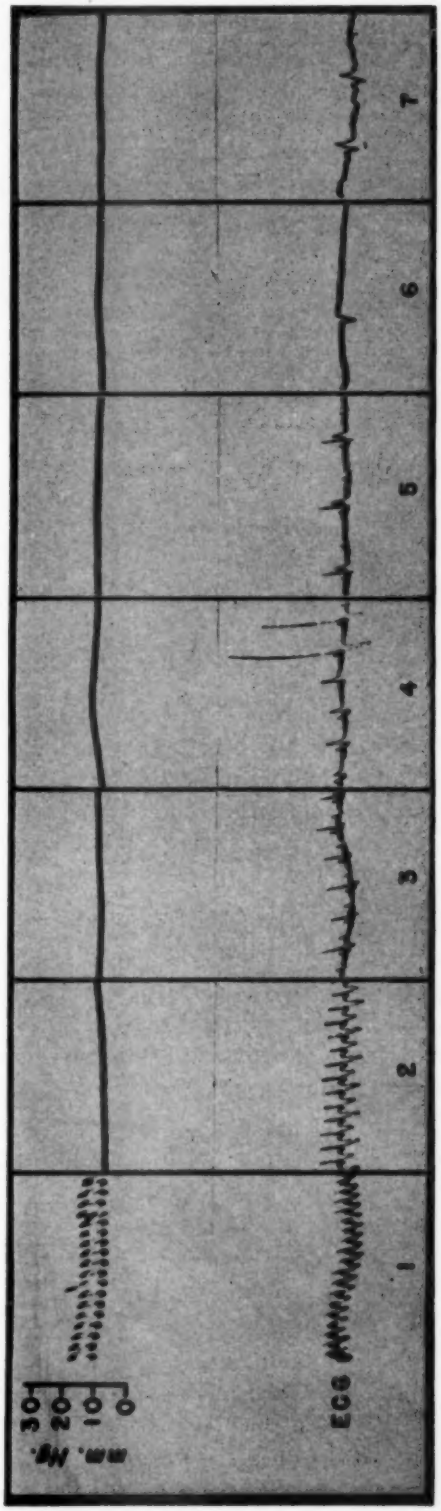

Fig. 2.—Serial intracardiac pressure and electrocardiographic recordings of the dying rabbit heart, animal No. 5. *1*, Previous to death; *2*, at death; *3*, 5.0 minutes; *4*, 5.5 minutes; *5*, 8.0 minutes; *6*, 11.5 minutes; *7*, 12.0 minutes after cessation of pulsatile changes.

muscle has been observed[9] to be negative with respect to normal muscle, and a sharp electrical boundary persists at the injured area of the zone of diastolic negativity.[10] Strong catelectrotonic effects of injury potential exist in this boundary zone which have been related to ectopic ventricular excitation.[11] The records of electrical activity observed during death in this study may be related to similar electrical and chemical changes associated with rapid muscle and conduction system degeneration.

TABLE II.

RABBIT	DURATION OF ECG AFTER ABSENCE OF PULSATILE CHANGE (MINUTES)	DURATION OF ECG AFTER ABSENCE OF VISIBLE CONTRACTIONS (MINUTES)	FINAL MECHANISM
A	8.5	4.0	Ventricular tachycardia and fibrillation
B	18.0	7.5	Ventricular fibrillation
C	0.75	0.75	Sinus bradycardia
D	14.5	10.0	4:1 heart block
E	23.0	18.0	Only P waves
F	1.0	1.0	3:1 heart block
G	2.0	1.5	Bradycardia
H	1.5	1.5	A-V block; ventricular fibrillation

Persistence of electrical complexes during the period of absent pulsatile change again demonstrates the lack of correlation between the electrocardiogram and the functional ability of heart muscle. Ventricular fibrillation as recorded may be a result rather than the cause of clinical death.

SUMMARY

Eighteen experiments on the dying rabbit heart have been studied by simultaneously recorded right ventricular pressures and Lead II electrocardiograms. The persistence of electrical activity beyond apparent clinical death of the animals, demonstrable right intraventricular pulsatile changes, and visible muscular contractions has been presented. Injury potentials associated with the degenerating heart may be a factor in the production of the electrocardiographic changes.

REFERENCES

1. Rhomer, H.: Ueber das Elektrokardiogramm des Diphtherieherztodes, München. med. Wchnschr. **58**:2358, 1911.
2. Turner, K. B.: Mechanism of Death of Human Heart as Recorded in Electrocardiogram, AM. HEART J. **6**:743, 1931.
3. Hanson, J. F., Purks, W. K., and Anderson, R. G.: Electrocardiographic Studies of Dying Human Heart, With Observations on Intracardiac Injection of Epinephrine, Arch. Int. Med. **51**:965, 1933.
4. Grieco, E. H., and Schwartz, S. P.: Observation on Mechanism of Dying Heart in Patient With Ventricular Tachycardia, AM. HEART J. **16**:595, 1938.
5. Goodrich, B. E., and Needles, R. J.: Terminal Cardiac Mechanism in Coronary Artery Disease; Report of Two Cases, AM. HEART J. **20**:637, 1940.
6. Krell, S.: Electrocardiographic Record of the Dying Heart, Ann. Int. Med. **21**:903, 1944.

7. Bukantz, S. C., Johnson, M. C., and Alexander, H. L.: Personal communication.
8. Lorente, D. R.: A Study of Nerve Physiology, Part I, New York, 1947, Rockefeller Institute for Medical Research.
9. Bayley, R. H., La Due, J. S., and York, D. J.: Electrocardiographic Changes Produced in Dogs by Temporary Occlusion of the Coronary Artery, Showing a New Stage in Evolution of Myocardial Infarction, AM. HEART J. **27**:164, 1944.
10. Sugarman, H., Katz, L. N., Sanders, A., and Jochim, K.: Observations On the Genesis of Electrical Currents Established by Injury to the Heart, Am. J. Physiol. **130**:130, 1940.
11. Harris, A. S.: Delayed Development of Ventricular Ectopic Rhythm Following Experimental Coronary Occlusion, Circulation **1**:1318, 1950.

THE USE OF PHARMACOLOGICAL TESTS IN THE DIAGNOSIS OF PHEOCHROMOCYTOMA

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ALTHOUGH recent reports have stressed the role of pheochromocytoma as a cause of hypertension, its accurate diagnosis remains a problem of considerable difficulty. Particularly since this is one type of hypertension which can be cured by surgical intervention, every effort should be made to recognize its presence. It is the purpose of this paper to call attention to the difficulties attending a clinical diagnosis of pheochromocytoma and to evaluate the usefulness of pharmacological tests advocated as an aid in the recognition of these chromaffin-cell tumors. A case is presented which demonstrates these points.

CASE REPORT

The patient was a 35-year-old white male seaman who entered the United States Marine Hospital, Staten Island, N. Y., on Jan. 24, 1950, because of severe headache intermittent since October, 1949. He had undergone yearly physical examinations for the past five years, the last being in July, 1949. No mention was made at any time of an elevated blood pressure. He was well until mid-October, 1949, when, after engaging in excessive physical activity he sat down to rest and was stricken with a severe throbbing frontal headache lasting about fifteen minutes, associated with a premonition of impending death. Thereafter almost daily recurrence of this headache was noted. A typical attack was characterized by a transient feeling of nausea, pounding in the stomach, pallor of the face, increased perspiration, muscular twitching of the face, and a feeling of blood rushing to the head preceding the severe headache. Exercise, excitement, sudden change of temperature, a full bladder, or the emptying of a full bladder were known to precipitate attacks.

Past history and family history were noncontributory, as was the review of systems.

Physical examination revealed a tall, lean, well-developed, and well-nourished white man in no distress at the time. Funduscopic examination revealed attenuation of the arterioles. The heart rate was 100 per minute. The blood pressure was 190/128 mm. Hg, but the remainder of the cardiovascular examination was normal. There were no palpable organs or masses in the abdomen. It was noted, however, that massage in the left upper quadrant was followed by an increase in the blood pressure to 230/150 mm. Hg accompanied by a typical mild attack. There were no other positive physical findings.

Laboratory examination of a twenty-four hour urine specimen revealed an albuminuria of 410 mg. The fasting blood sugar varied from 85 to 136 mg. per cent. The Mosenthal test, glucose tolerance, hematological examination, blood electrolytes and nonprotein nitrogen, as well as liver function, tests were within normal limits.

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Roentgenograms of the chest including cardiac fluoroscopy were within normal limits. Excretory urography revealed poor function on the left side; a repeat examination one month later revealed poor function bilaterally. Tomography of the upper abdomen revealed no abnormality. The basal metabolic rate was +18 per cent. Electrocardiographic studies were normal. The blood pressure was determined twice daily and was found to vary from 130 to 230 mm. Hg systolic and from 80 to 150 mm. Hg diastolic (Fig. 1).

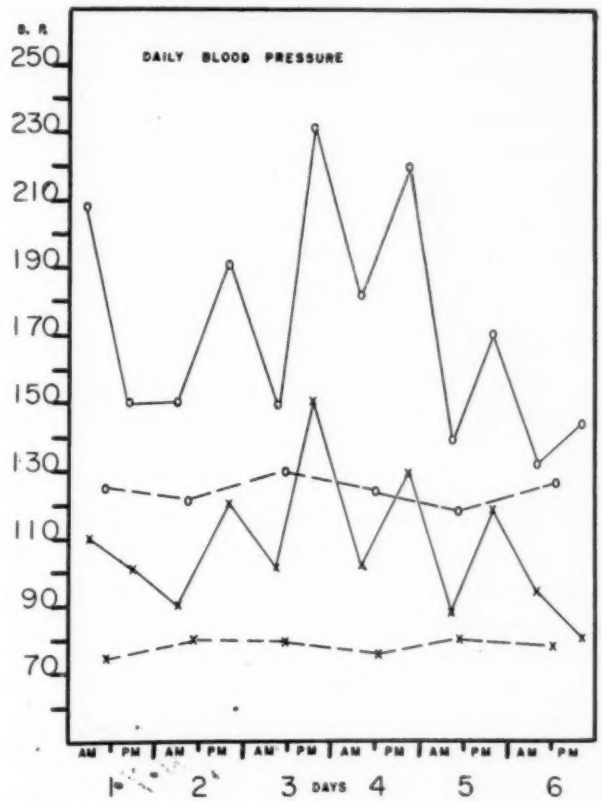

Fig. 1.—Daily blood pressure. O= systolic pressure; X = diastolic pressure; ———preoperatively; – – – postoperatively. The patient experienced spontaneous, paroxysmal attacks on days one, three, and four preoperatively.

Although the history, physical examination, and laboratory findings suggested the diagnosis of pheochromyocytoma, it was felt that the employment of pharmacological tests would aid in reaching a more definitive conclusion. The benzodioxane test was carried out twice and was negative on each occasion. The histamine test for pheochromocytoma was strongly positive, the reaction to the intravenous injection of 0.025 mg. being more severe than any spontaneous attack. The tetraethylammonium chloride test was positive; the Mecholyl test was negative as was the cold pressor test. The Sodium Amytal sedation test was carried out by giving 7½ grains of Sodium Amytal orally and determining the blood pressure at repeated intervals. The pressure dropped in one hour from 160/80 to 135/78 mm. Hg.

Since the pharmacological tests confirmed the clinical impression of pheochromocytoma, the patient was transferred to the surgical service.

Anesthesia was induced by means of intravenous Pentothal followed by nitrous oxide and ether. He was given oxygen continuously and cyclopropane intermittently during the surgical procedure; 0.4 per cent procaine was given intravenously to prevent cardiac arrhythmia. Since

massage in the left upper quadrant was followed by an elevation of blood pressure and a mild attack, it was decided to explore this region first. Consequently, a left lumbar incision was made, and a tumor was found at the upper pole of the left kidney partially surrounded by adrenal tissue. It was of the same general color and consistency as the kidney and at first was not recognized as a separate structure. As the tumor was manipulated, the blood pressure rose from 200/110 to 230/125 mm. Hg. Ten milligrams of benzodioxane were given intravenously with a subsequent drop in blood pressure to 170/90 mm. Hg. As the vessels surrounding the tumor were being ligated, the pressure again rose to 210/100 mm. Hg. Another injection of 20 mg. of benzodioxane was then given. Immediately after this injection, the larger veins of the tumor were ligated, and the blood pressure dropped precipitously to 90/60 mm. Hg, but rose immediately to 130/85 mm. Hg. The blood pressure was supported by the injection of 20 mg. of methoxamine and varied from 120 to 130 mm. Hg systolic and from 70 to 80 mm. Hg diastolic for the remainder of the operation. It was not necessary to give either epinephrine or adrenal cortical extract postoperatively. The patient's postoperative course was uncomplicated. The blood pressure varied from 118 to 130 mm. Hg systolic and from 72 to 82 mm. Hg diastolic (Fig. 1). The histamine and tetraethylammonium tests following operation were negative.

The specimen removed at operation measured 6½ by 4½ by 4 cm. and weighed 40 grams. On cut section there was evidence of scarring and small hemorrhagic areas. Microscopically the tumor was seen to be well encapsulated and to arise from the medullary substance of the adrenal; it was distinctly separated from the intact zona fasciculata and zona glomerulosa. The tumor cells were arranged in an alveolar pattern; the individual cells were large, polyhedral, and contained heavy brown granules in the cytoplasm. The nuclei were round or oval with dark nucleoli; mitoses were rarely seen. The pathological diagnosis was pheochromocytoma, benign, of the adrenal gland.*

DISCUSSION

Pheochromocytomas may be found in practically every region of the body, but most commonly in the adrenals and the organ of Zuckerkandl. Tumors in other regions are usually asymptomatic.[1-5]

The first case of pheochromocytoma was recorded in 1886 when Frankel[6] found bilateral adrenal tumors in an 18-year-old girl. The correct ante-mortem diagnosis of pheochromocytoma, however, was not made until 1926.[8] In 1929, Pincoffs[10] reported the correct preoperative diagnosis of pheochromocytoma and the successful removal of the tumor. In 1937, Beer, King, and Prinzmetal[11] demonstrated increased amounts of circulating epinephrine in a patient with pheochromocytoma, but they were unable to repeat this observation postoperatively. The full description of the signs and symptoms of pheochromocytoma was published in 1922[7]; these have been listed in the literature with additions many times since.[1-5,8-11,18,22-28,38,42] Smithwick recently compared the symptoms and signs useful in differentiating pheochromocytoma and essential hypertension.[4]

In addition to the classical symptomatology, attention has been called to the fact that a significant number of patients with pheochromocytoma may have a persistent hypertension and present the findings typical of essential hypertension.[4,14,20-24,26,29] In a review of the literature by Green[29] twenty-seven of fifty patients presented a persistent hypertension; however, some of these had paroxysmal attacks. In 1,000 hypertensive patients undergoing lumbodorsal sympathectomy for hypertension, Smithwick[4] found five cases of pheochromocytoma.

*Pathology examination and report by Dr. Lawrence Sophian, Chief, Department of Pathology, United States Public Health Service Hospital, Staten Island, N. Y.

The hypothesis of circulating epinephrine being the cause of both the paroxysmal and the sustained type of hypertension has not been acceptable to many authors. This concept was clarified in 1949 by Holton[19] when it was shown in three cases of pheochromocytoma that the tumor contained 63, 93, and 94 per cent nor-epinephrine, respectively. This important finding was confirmed by Goldenberg, Faber, Alston, and Chargaff[31] in three tumors from patients with pheochromocytoma. That the various amounts of the two types of epinephrine do influence the clinical findings was recently shown by Goldenberg and Aranow.[20,47] The clinical data were correlated with the nor-epinephrine and l-epinephrine content of ten tumors from patients with persistent hypertension and four tumors from patients with paroxysmal hypertension. "When the tumor contains epinephrine predominantly, or a very large amount of nor-epinephrine, the picture is characterized by hypertension, tachycardia, hyperhidrosis, hypermetabolism and frequently hyperglycemia. When the tumor is small and contains for practical purposes nor-epinephrine only, the syndrome of essential hypertension is very closely mimicked."[20]

Pharmacological Tests.—Because of the difficulties in arriving at a definitive diagnosis by means of the routine history and physical examination, a number of pharmacological tests have been suggested. Benzodioxane, dibenamine, and C 7337 have been employed as depressor tests. The pressor tests are histamine, tetraethylammonium, and Mecholyl.

The benzodioxane compounds were studied in 1933[13] and found to possess an action antagonistic to that of adrenaline. In 1947, Goldenberg, Snyder, and Aranow[14] found that the intravenous injection of 0.25 mg. per kilogram of 933F in patients with pheochromocytoma was followed by a drop in both systolic and diastolic pressure of about 60 mm. Hg lasting for ten to fifteen minutes. When similar amounts were given patients with essential hypertension, a slight pressor effect was noted, thus demonstrating that, in this amount, benzodioxane was adrenolytic but not sympatholytic.

Although benzodioxane is an adrenolytic agent, its precise mode of action is not definitely known. It has been suggested that benzodioxane does not render the effector cells impermeable, but accelerates the inactivation of epinephrine.[48] Raab[44,46] has shown that benzodioxane prevents the fatal accumulation of injected epinephrine in the myocardium of animals.

Our patient with pheochromocytoma was given 20 mg. of benzodioxane intravenously on two occasions; only a slight pressor effect was noted (Fig. 2). The reason for the negative benzodioxane test is not clear. It may be that the benzodioxane was not injected at a time when the patient manifested an excess of circulating epinephrine. This suggestion is supported by the fact that benzodioxane depressed the blood pressure following tumor manipulation at operation. Raab[44,46] has pointed out that as an antiepinephrine agent benzodioxane is inferior to both dibenamine and Priscol. Attention has also been called to the fact[45] that the degree of inhibition of epinephrine by benzodioxane is proportional to the amount of drug used and can be overcome by an increase in the concentration of epinephrine.

The benzodioxane test has been used in many cases of pheochromocytoma.[18,22,23,26,30,33-35] The case herein reported is the eighth instance of a false-negative test in the literature.[22,26,30,33,50] Three false-positive benzodioxane tests are recorded; one was in a patient with renal hypertension,[36] one in a patient with uremia,[34] and the third in a patient with a neuroblastoma.[45] However, the test was considered as of sufficient value to be performed routinely on every hypertensive patient admitted to one institution.[26] A word of caution should be noted regarding the use of benzodioxane. No irreversible effects have been recorded; however, rather alarming pressor reactions in hypertensive patients and one instance of hypertensive encephalopathy have been induced by benzodioxane.[22,50]

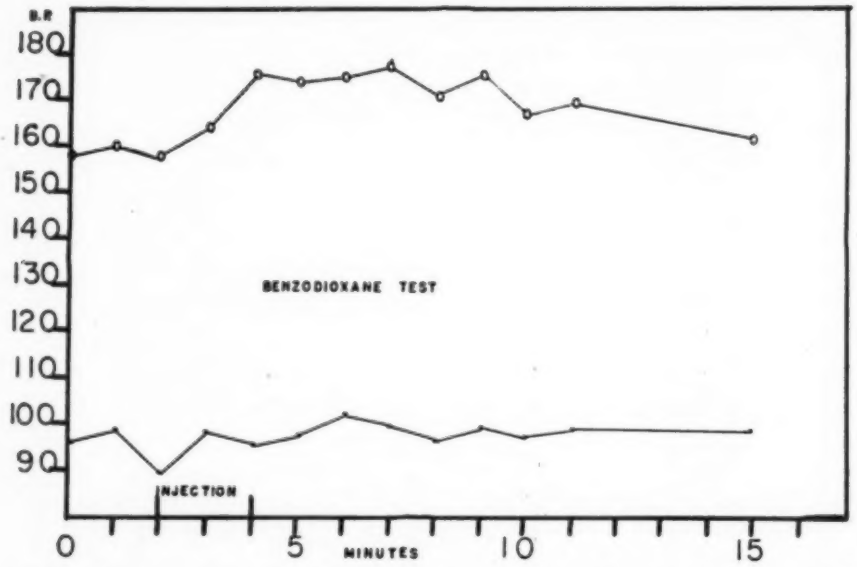

Fig. 2.—Benzodioxane test. O = systolic pressure; ● = diastolic pressure. Twenty mg. of benzodioxane were injected intravenously over the two-minute period from two to four minutes.

Dibenamine was extensively studied by Hecht and Anderson[15] and was used as a depressor agent in pheochromocytoma in 1948.[38] In addition to the depression of the blood pressure, dibenamine will prevent the pressor response to histamine.[37,38] However, the depression is not specific for pheochromocytoma since a similar effect is seen in both normal and hypertensive individuals. We did not use dibenamine because of its reported toxic effects, such as phlebothrombosis, nausea, psychosis, convulsions, excessive drowsiness, and dizziness.[15]

An adrenolytic drug, 2 (N, p-tolyl-N [m′ hydroxyphenyl]- aminoethyl)-imidazoline hydrochloride, or C 7337, has been used by Grimson and associates[19,34] and was found to be most satisfactory for controlling the blood pressure fluctuations during surgical removal of pheochromocytoma. This agent was not sympatholytic in the dosage used.

Histamine was first given to a patient with pheochromocytoma in 1927 when Mayo[9] used it in an attempt to abort a spontaneous attack. Whether or not a pressor response was elicited is not recorded. In 1943, Hyman and Mencher

(quoted by Roth and Kvale[12]) produced an attack by the injection of histamine and also by the performance of the cold pressor test. In 1945,[12] Roth and Kvale proposed the intravenous use of histamine as a diagnostic test for pheochromocytoma. In their original series of three cases the response to histamine was an elevation of about 100 mm. more in the systolic blood pressure than the response to the cold pressor test. This difference is not necessary for a positive test, as attacks have been induced by the cold pressor test.[12]

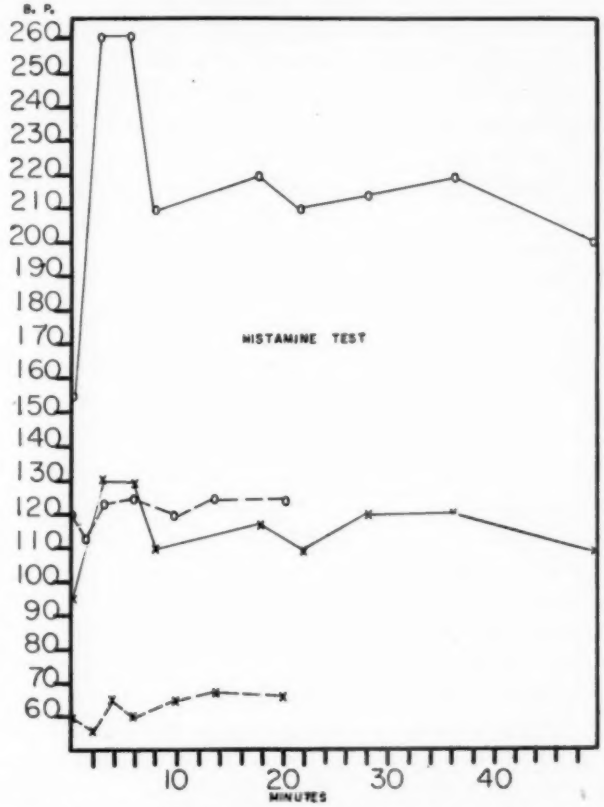

Fig. 3.—Histamine test. O = systolic pressure; ● = diastolic pressure;————preoperatively; - - - - -postoperatively. The sphygmomanometer was calibrated only to 260 mm. Hg, so that the maximum systolic pressure was not obtained preoperatively.

It has been suggested that histamine brings about a dilatation of arterioles and capillaries of the tumor with a subsequent release of epinephrine.[17] However, the same authors stated that perhaps histamine has a direct stimulating effect upon the chromaffin tumor cells somewhat similar to its action on the chief cells of the stomach. The histamine test was performed in our patient (Fig. 3), and an immediate rise in blood pressure was noted following the intravenous injection of this agent. Unfortunately, the sphygmomanometer was calibrated to only 260 mm. so that the maximum pressure was not obtained. The patient experienced a severe headache, became quite red in the face, and was unable to lie quietly in bed; a profuse diaphoresis was noted. Postoperatively, a negative test was found following the intravenous administration of histamine (Fig. 3).

The histamine test has been employed in a number of instances,[12,16,17,22,25,26,33,35,39,49,50] and no serious effects have been noted. In one instance, however, Wilkins and co-workers[22] felt that had a satisfactory depressor agent not been available, the histamine would have induced serious effects in their patient. Negative postoperative histamine tests have been recorded in two instances in addition to the reported case.[17, 9] Six false-negative[26, 5,49,50] and "a number" of false-positive[26,50] histamine tests have been reported.

In 1948, La Due, Murison, and Pack[17] gave 400 mg. of tetraethylammonium bromide intravenously to a patient with pheochromocytoma, hoping to produce a depressor effect; however, a marked pressor response was obtained. They also noted that when the patient was changed from the supine to the standing position, the blood pressure fell from 230/125 to 95/80 mm. Hg. The authors pointed to this means of terminating an attack as a distinct advantage over the histamine test. The test was repeated after operation and was negative. They suggested that tetraethylammonium (TEA) acted by blocking the autonomic ganglia with a resultant denervation of the blood vascular supply of the tumor; thus vasodilation increased blood flow to the tumor with an outpouring of epinephrine into the peripheral circulation. A direct stimulating effect upon the chromaffin cells was considered unlikely since they found the pressor effect to be manifest within thirty seconds of the injection. In 1947, [9] Page and Taylor presented a seemingly more logical explanation when they observed that the injection of tetraethylammonium potentiated the pressor action of injected epinephrine and angiotonin. Moe[40] confirmed and extended this observation by demonstrating the potentiation of both pressor and depressor substances following the injection of TEA and noted the similarity to an animal in which the spinal cord and medulla had been destroyed. The potentiation of pressor and depressor substances is due to the blockade of sympathetic ganglia and the carotid and aortic regulatory ganglia. This augmentation by TEA has recently been demonstrated in man by Page and Taylor using 500 mg. of the drug.[41] The observation of Console and associates[42] that tachycardia accompanied the TEA-induced attack in a patient with pheochromocytoma, whereas the spontaneous attack was usually accompanied by bradycardia, is in keeping with the previously mentioned proposal. The fact that smaller amounts of TEA did not have a pressor effect in our patient and that 400 mg. definitely did supports this explanation for the mechanism of action of TEA in patients with pheochromocytoma.

We were hesitant initially to give our patient 400 mg. of tetraethylammonium chloride in a single intravenous injection. Consequently, he was given 100 mg. intravenously at two-minute intervals until 400 mg. had been given. This was followed by a drop of 20 mm. in the systolic blood pressure and of 10 mm. in the diastolic. The following day he was given 400 mg. intravenously in a single injection, and a typical pressor response followed with maximal effect four minutes after injection. The test was repeated postoperatively with only a slight depressor effect (Fig. 4).

TEA has been used in several cases of pheochromocytoma since the original report.[26,33,35,49] The pressor effect has been shown to be abolished by a previous injection of benzodioxane.[35] Two false-positive and three false-negative tests have been reported.[33,49]

Guarneri and Evans[16] gave Mecholyl subcutaneously to a patient with pheochromocytoma, hoping to depress the blood pressure; however, a pressor effect was produced. The administration of 1/75 grain of atropine prevented the muscarinic side effects of Mecholyl, but did not affect the pressor response.

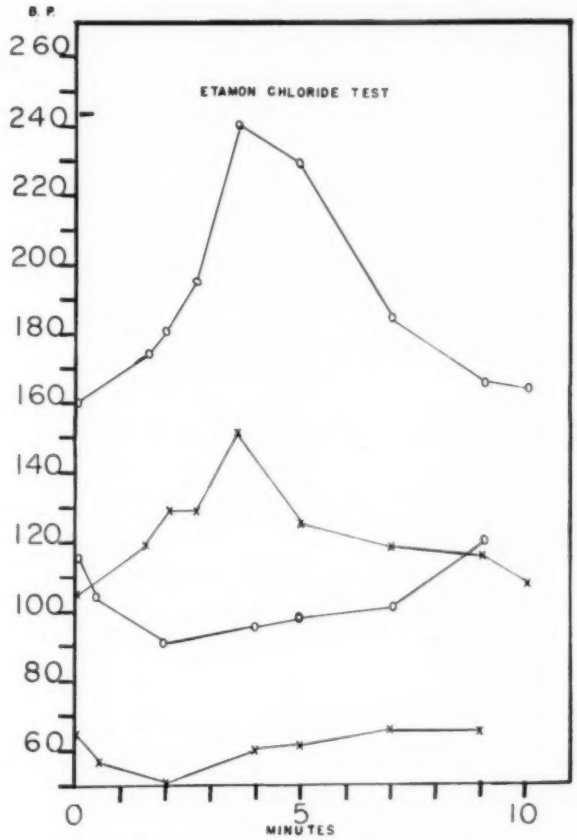

Fig. 4.—TEA (Etamon*) test. O = systolic pressure; X = diastolic pressure. The two top curves are the preoperative test; the bottom two curves are the postoperative test.

The Mecholyl test was performed on two occasions preoperatively in our patient by the subcutaneous injection of 25 mg. of Mecholyl. Both before and after operation, a rather moderate depressor effect occurred (Fig. 5). Mecholyl has been employed in three other cases[35,49] since the original publication. A positive response was obtained in one.[49] It has been suggested that atropine be given to all patients undergoing the Mecholyl test since 25 mg. is supposed to have caused fatal reactions.

Thus, pharmacological tests appear to be an aid in the diagnosis of pheochromocytoma. This would seem to be further confirmed by the group of eleven patients with pheochromocytoma reported by Smithwick and co-workers[4] in whom the diagnosis was made on clinical grounds in only three. The remainder were found by palpation of the adrenal region while the patient

*Trademark of Parke, Davis & Company, Detroit, Mich.

was undergoing splanchnicectomy for hypertensive cardiovascular disease. We thus feel that every case of sustained, as well as paroxysmal, hypertension should be evaluated for pheochromocytoma, especially if a major operation is contemplated. This evaluation should include, in addition to the history, physical examination, and routine laboratory studies, a battery of pharmacological tests such as was done in the present case. Of these tests, the benzodioxane has had the widest trial and is to be recommended in cases of sustained hypertension. Both false-positive and false-negative tests have been reported with benzodioxane, TEA, and histamine. Only one positive Mecholyl test[49] has been recorded since the original communication of Guarneri and Evans.[16] It is thus obvious that there is no specific test for pheochromocytoma.

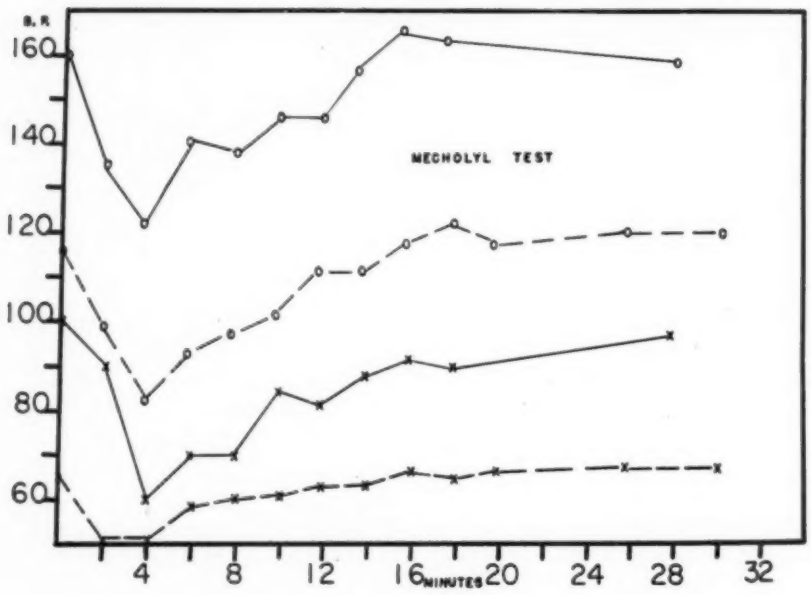

Fig. 5.—Mecholyl test. O = systolic pressure; X = diastolic pressure; ———preoperatively; - - - - -postoperatively.

In addition to the surgical skill necessary for the proper conclusion of the treatment of a case of pheochromocytoma, the role of the anesthetist should not be minimized. Those patients on whom an adrenolytic substance has been used by the anesthetist during operation have not suffered appreciably from shock as is so often the case after removal of these tumors. The agent of choice would seem to be C 7337 described by Grimson and associates[18,34] since its toxicity is low and its effect is more prolonged than the other suggested agents.

CONCLUSIONS

It is concluded that there is no single pharmacological test for pheochromocytoma, but that the definitive diagnosis will rest upon the usual clinical evaluation of the patient and the results of a battery of tests. This battery is composed

of the tetraethylammonium, the histamine, the benzodioxane, and the C 7337 tests. The Mecholyl test should also be done in known cases, so as to evaluate further its usefulness.

We feel that all cases of either sustained or paroxysmal hypertension should be studied for the presence of pheochromocytoma, especially if a major operation is contemplated. In this way an occasional patient will be cured of this surgically reversible type of hypertension.

SUMMARY

1. A partial review of the literature concerning pheochromocytoma is presented.

2. A patient in whom the correct diagnosis was made preoperatively and the tumor successfully removed is discussed.

3. Attention is called to the variability of the clinical picture associated with pheochromocytoma and its correlation with the type of epinephrine elaborated by the tumor.

4. The benzodioxane, histamine, tetraethylammonium, and Mecholyl tests are reviewed and evaluated in the reported case.

5. An explanation for the mechanism of action of tetraethylammonium in pheochromocytoma is advanced.

6. It is concluded that a battery of pharmacological tests has a definite and useful place in the diagnosis of pheochromocytoma.

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REFERENCES

1. Hatch, F. N., Richards, V., and Spiegel, R. J.: Adrenal Medullary Tumor (Pheochromocytoma), Am. J. Med. **6**:533, 1949.
2. Hyman, A., and Mencher, W. H.: Pheochromocytoma of the Adrenal Gland, J. Urol. **49**:755, 1943.
3. Belt, A. E., and Powell, T. O.: Clinical Manifestations of the Chromaffin Cell Tumors Arising From the Suprarenal Medulla-Suprarenal Sympathetic Syndrome, Surg., Gynec. & Obst. **59**:9, 1934.
4. Smithwick, R. H., Greer, W. E. R., Robertson, C. W., and Wilkins, R. W.: Pheochromocytoma; A Discussion of Symptoms, Signs and Procedures of Diagnostic Value, New England J. Med. **242**:252, 1950.
5. Mackeith, R.: Adrenal-Sympathetic Syndrome; Chromaffin Tissue Tumor With Paroxysmal Hypertension, Brit. Heart J. **6**:1, 1944.
6. Frankel, F.: Ein Fall von doppelsteitigem, vollig latent verlaufenen Nebennierentumor und gleichzeitiger Nephritis mit Veranderungen am Circulationsapparat und Retinitis, Virchows Arch. f. path. Anat. **103**:244, 1886.
7. Labbé, M., Tinel, J., and Doumer: Crises solaires, et hypertension paroxystique en rapport avec une tumeur surrenale, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:982, 1922.
8. Vaquez, H., and Donzelot, E.: Les crises d'hypertension arterielle paroxystique, Presse méd. **34**:1329, 1926.
9. Mayo, C. H.: Paroxysmal Hypertension With Tumor of Retro-peritoneal Nerve, J. A. M. A. **89**:1047, 1927.
10. Pincoffs, M. C.: A Case of Paroxysmal Hypertension Associated With Suprarenal Tumor, Tr. A. Am. Physicians **44**:295, 1929.

11. Beer, E., King, F. H., and Prinzmetal, M.: Pheochromocytoma With Demonstration of Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crises, Ann. Surg. **106**:85, 1937.

12. Roth, G. M., and Kvale, W. F.: A Tentative Test for Pheochromocytoma, Am. J. M. Sc. **210**:5, 1945.

13. Fourneau, E., and Bovet, D.: Recherches sur l'action sympathicolytique d'un nouveau dérivé du dioxane, Arch. internat. de pharmacodyn. et de thérap. **46**:178, 1933.

14. Goldenberg, M., Snyder, C. H., and Aranow, H., Jr.: New Test for Hypertension due to Circulating Epinephrine, J. A. M. A. **135**:971, 1947.

15. Hecht, H. H., and Anderson, R. B.: The Influence of Dibenamine (N,N-Dibenzyl-B-Chloroethyl-Amine) on Certain Functions of the Sympathetic Nervous System in Man, Am. J. Med. **3**:3, 1947.

16. Guarneri, V., and Evans, J. A.: Pheochromocytoma; Report of a Case, With a New Diagnostic Test, Am. J. Med. **4**:806, 1948.

17. La Due, J. S., Murison, P. J., and Pack, G. T.: The Use of Tetraethylammonium Bromide as a Diagnostic Test for Pheochromocytoma, Ann. Int. Med. **29**:914, 1948.

18. Grimson, K. S., Longino, F. H., Kernodle, C. E., and O'Rear, H. R.: Treatment of a Patient With a Pheochromocytoma; Use of an Adrenolytic Drug Before and During Operation, J. A. M. A. **140**:1273, 1949.

19. Holton, P.: Nor-Adrenaline in Adrenal Medullary Tumors, Nature **163**:217, 1949.

20. Goldenberg, M., and Aranow, H., Jr.: Pheochromocytoma and Essential Hypertension (Abstract), J. Clin. Investigation **29**:816, 1950.

21. Thorn, G. W., Hindle, J. A., and Sandmeyer, J. A.: Pheochromocytoma of the Adrenal Associated With Persistent Hypertension: Case Report, Ann. Int. Med. **21**:122, 1944.

22. Wilkins, R. W., Greer, W. E. R., Culbertson, J. W., Halperin, M. H., Litter, J., Burnett, C. H., and Smithwick, R. H.: Extensive Laboratory Studies of a Patient With Pheochromocytoma Before and After Successful Operation With a Note on the Trial of Piperidylmethyl Benzodioxane to Differentiate Such Conditions From Essential Hypertensive Vascular Disease, Arch. Int. Med. **86**:51, 1950.

23. Snyder, C. H., and Vick, E. H.: Hypertension in Children Caused by Pheochromocytoma; Report of Three Cases and Review of the Literature, Am. J. Dis. Child. **73**:581, 1947.

24. Spatt, S. D., and Grayzel, D. M.: Pheochromocytoma of the Adrenal Medulla; A Clinicopathological Study of Five Cases, Am. J. M. Sc. **216**:39, 1948.

25. De Vries, A., Rachmilewitz, M., and Schumert, M.: Pheochromocytoma With Diabetes and Hypertension; Report of Two Cases Cured by Operation, Am. J. Med. **6**:51, 1949.

26. Aranow, H., Jr.: The Differential Diagnosis of Pheochromocytoma, M. Clin. North America **34**:757, 1950.

27. Howard, J. E., and Barker, W. H.: Paroxysmal Hypertension and Other Clinical Manifestations Associated With Benign Chromaffin Cell Tumors (Pheochromocytomata), Bull. Johns Hopkins Hosp. **61**:371, 1937.

28. Brunschwig, A.: Paroxysmal Hypertension From Pheochromocytoma, J. A. M. A. **134**:253, 1947.

29. Green, D. M.: Pheochromocytoma and Chronic Hypertension, J. A. M. A. **131**:1260, 1946.

30. Goldenberg, M., and Aranow, H.: Diagnosis of Pheochromocytoma by the Adrenergic Blocking Action of Benzodioxane, J. A. M. A. **143**:1139, 1950.

31. Goldenberg, M., Faber, M., Alston, E. J., and Chargaff, E. C.: Evidence for the Occurrence of Nor-Epinephrine in the Adrenal Medulla, Science **109**:534, 1949.

32. Goldenberg, M., Pines, K. L., Baldwin, E. D. F., Green, D. G., and Roh, C. E.: The Hemodynamic Response of man to Nor-Epinephrine and Epinephrine and Its Relation to the Problem of Hypertension, Am. J. Med. **5**:792, 1948.

33. Roth, G. M., and Kvale, W. F.: Pharmacologic Tests as an Aid in Diagnosis of Pheochromocytoma Mod. Concepts Cardiovas. Dis. **18**:41, 1949.

34. Grimson, K. S., Lyons, C. K., Wortham, J. T., and Hambleu, E. C.: Observations Using Adrenolytic Drugs and Surgery for Tumors of the Adrenal Gland (Abstract), J. Clin. Investigation **29**:819, 1950.

35. Shapiro, A. P., Baker, H. W., Hoffman, M. S., and Ferris, E. B.: Physiologic and Pharmacologic Studies in a Case of Pheochromocytoma (Abstract), J. Lab. & Clin. Med. **34**:1751, 1949.

36. Taliaferro, I., Adams, R. A., and Haag, H. B.: Benzodioxane Test; Fall in Blood Pressure Following Its Use in a Case of Renal Hypertension, J. A. M. A. **140**:1271, 1949.

37. Spear, H. C., and Griswold, D.: The Use of Dibenamine in Pheochromocytoma, New England J. Med. **239**:736, 1948.

38. Hoch, G. F.: Pheochromocytoma With Paroxysmal Hypertension, J. Urol. **61**:473, 1949.

39. Page, I. H., and Taylor, R. D.: Sensitization to the Pressor Action of Epinephrine, J. A. M. A. **135**:348, 1947.

40. Moe, G. K.: Potentiation of Pressor Action of Epinephrine by Tetraethylammonium, J. A. M. A. **137**:1115, 1948.

41. Page, I. H., and Taylor, R. D.: Augmentation of Vasoactive Substances by Tetraethylammonium Chloride, Circulation **1**:1233, 1950.

42. Console, A. D., Dunbar, H. S., and Ray, B. S.: Pheochromocytoma, Surgery **28**:428, 1950.

43. Smithwick, R. H.: Personal communication to Goldenberg, M., Snyder, C. H., and Aranow, H., Jr.[14]

44. Raab, W.: Adreno-sympathogenic Heart Disease (Neurohormonal Factors in Pathogenesis and Treatment), Ann. Int. Med. **28**:1010, 1948.

45. Calkins, E., Dana, G. W., Seed, J. C., and Howard, J. E.: On Piperidylmethyl Benzodioxane (933F); Hypertension and Pheochromocytoma. In press. (Referred to by Wilkins and associates.[22])

46. Raab, W., and Humphreys, R. J.: Protective Effect of Adrenolytic Drugs Against Fatal Myocardial Epinephrine Concentrations, J. Pharmacol. & Exper. Therap. **88**:268, 1946.

47. Goldenberg, M., Aranow, H., Jr., Smith, A. A., and Faber, M.: Pheochromocytoma and Essential Hypertensive Vascular Disease, Arch. Int. Med. **86**:823, 1950.

48. Morison, R. S., and Lissak, K.: Observation on the Mode of Action of Piperidinomethylbenzodioxane (933F), Am. J. Physiol. **123**:404, 1938.

49. Bartels, E. C., and Cattell, R. B.: Pheochromocytoma: Its Diagnosis and Treatment, Ann. Surg. **131**:903, 1950.

50. Calkins, E., Dana, G. W., and Howard, J. E.: Current Methods of Diagnosis of Pheochromocytoma, J. A. M. A. **145**:880, 1951.

INTRA-ARTERIAL INFUSION IN THE TREATMENT OF SHOCK RESULTING FROM CORONARY OCCLUSION*

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WHENEVER shock occurs after coronary occlusion, the prognosis at once becomes more grave, calling for vigorous measures to elevate the arterial pressure. The over-all mortality rate among patients with recent myocardial infarction with shock is 80 per cent, and the prognosis is worse when the systolic pressure falls to 80 mm. Hg or less.[1-5] The degree and duration of shock bear a further direct relationship to the rate of mortality, and patients in profound shock rarely recover. We have used, in such cases, intra-arterial infusion which, in addition to combating shock, has the special action of increasing coronary flow by the direct effect of elevating aortic pressure.

The main reason, probably, for the serious import of shock in coronary occlusion is the further reduction of coronary flow to normal myocardium due to the fall in arterial pressure.[6,7] After experimental coronary ligation the ischemic myocardium ceases to contract and tends to bulge during systole.[8] This area of ischemia and the aneurysmal dilatation become more extensive at lowered arterial pressures because of the decrease or cessation of flow through the collateral coronary arteries.[9] Such functioning collaterals have been well demonstrated in dogs and human normal and arteriosclerotic hearts with myocardial infarction.[10,11] The decrease in coronary flow due to hypotension and that due to coronary obstruction summate to effect greater loss of contracting myocardium. This establishes a vicious cycle leading to progressively decreasing myocardial action.

Shock per se produces fatty change and necrosis of myocardial fibers, the intensity of change increasing with the severity of shock.[12,13] This myocardial deterioration probably due to inadequate coronary circulation is believed itself to contribute to the general circulatory failure and ultimate irreversibility of the condition.[14] Shock, therefore, adversely affects also uninfarcted myocardium. In the absence of shock, the uninfarcted myocardium often exhibits a striking ability to compensate by dilatation for the partial loss of functioning myocardium. This is well borne out by the frequency with which elevated pressures are maintained in the face of infarction or extensive fibrosis. Such remarkable reserve power has also been demonstrated experimentally.[15] But in the presence of shock the heart cannot utilize fully this reserve power and may be unable to compensate

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for infarction. We agree with Boyer's concept[16] that when shock occurs at the onset of the attack, "the resultant fall in blood pressure may so diminish blood flow in the unoccluded coronary arteries as to depress the uninfarcted muscle, thus preventing its normal compensatory response. The result would then be progressive hypodynamic heart action and shock persisting beyond the usual duration of primary shock." To maintain the function of the uninfarcted muscle and decrease the extent of infarction, arterial pressure must be restored; to minimize the irreparable damage and anticipate the irreversible state that may ensue, efforts to elevate the arterial pressure must be direct and prompt.

In recent years intra-arterial infusion has been found the most rapid and direct method of restoring arterial pressure in hemorrhagic shock.[17-19] Experimentally little more than one-half the amount of blood is required to restore arterial pressure than when blood is given by vein.[18] Page[19] has pointed out, also, that intra-arterial infusion provides an auxiliary pump to help fill the vascular tree and maintain pressure in it.

On the basis of the preceding rationale, we prepared for the treatment of coronary shock by intra-arterial infusion of blood or plasma after first testing the safety of our apparatus in animals and observing no ill effects from it in normal individuals.

METHOD

The importance of certain objectives in the method soon becomes obvious. One must aim for simplicity in the apparatus and the procedure offering the least loss of time and waste of effort.

Our initial apparatus was discarded in favor of a simple two-piece set, an inlet attached to a pressure bulb, and a one-piece outlet incorporating a plastic chamber, filter, and tube. The inlet requires only a ring-necked needle to assure a tight fit in the cap of the fluid container. The outlet must be of nonelastic construction, rigidly joined, and tightly fitting into the cap.* The present set has presented none of the difficulties of clotting and leakage so frequent in our initially more pretentious model. Although the present model does not include the means of making pressure recordings, as originally planned in this work, we have found that the precarious state of the patients thus far presented for treatment has afforded no time for such determinations.

Attempts at femoral artery puncture have also been replaced, almost routinely, by brachial artery cut-down. Femoral pulsations in this type of case are usually either absent or evanescent and too often a decoy leading to fruitless effort. Absent pulsations and cyanosis make it almost impossible to enter the femoral artery via skin puncture with certainty of the location of the needle.

RESULTS

The eight patients in this series with myocardial infarction were in severe to profound shock for three to twenty-eight hours before they received intra-

*We have found that the plastic set of Cutter and Co., who kindly provided the apparatus used in our latter cases, most nearly fills these requirements and is capable of sustaining pressures adequate for our purpose.

arterial infusions. Up to 1,000 c.c. of blood or plasma were given at a rate, generally, of 75 to 100 c.c. per minute. Six of these patients showed evidence of improvement as manifested by the heart sounds, respirations, degree of pain, and the electrocardiogram. Elevation of blood pressure occurred in four patients in whom infusion seemed effective in enabling them to survive critical periods of shock for hours, days, or months (eight hours, eleven and fourteen days, and one surviving after ten months, respectively). There was no increase in pulmonary congestion during the infusion even though pulmonary congestion was already present in one. One patient developed ventricular fibrillation shortly after infusion. Generally, results improved as greater facility in technique was achieved.

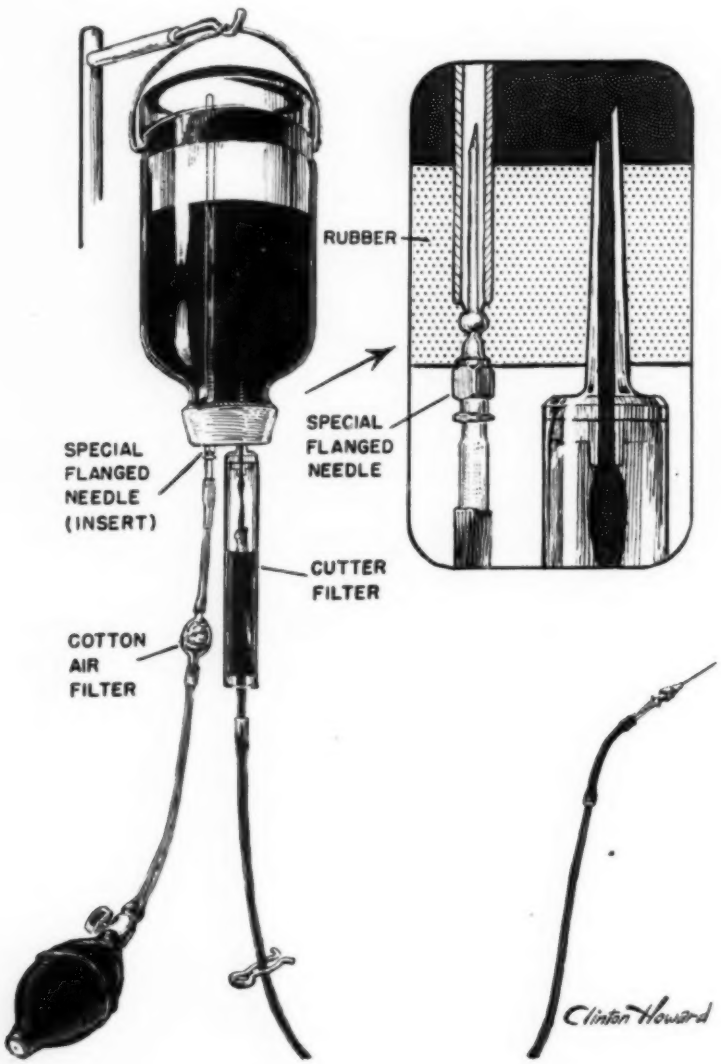

Fig. 1.

COMMENT

Elevation of arterial pressure became manifest about twenty to forty minutes after completion of the infusion and continued to rise slowly for one to three hours. This "delayed" response suggests that arterial infusion initiates a second process resulting in improved heart action. The course of these patients indicates that after treatment the margin of reserve is narrow for a variable period. Other methods of increasing the compensatory reserve should be utilized when indicated. For example, the additional procedure of phlebotomy may be necessary. Myocardial reserve is increased by decreasing the volume of an overdilated heart. Since pulmonary edema may constitute a more immediate threat to life than shock, the treatment of marked pulmonary congestion due to venous engorgment should receive precedence. Thus, it is our impression that Patient F. G. with marked pulmonary congestion might have been further improved if phlebotomy had been carried out, but unsuccessful attempts were made to draw blood from collapsing antecubital veins when the femoral vein would have been the wiser approach.

While the myocardial reserve is still narrow, recurrence of hypotension may again readily precipitate circulatory failure, requiring repetition of arterial infusion. We feel that the patients who were helped to survive initial episodes of critical hypotension may have been able to recover from subsequent attacks if intra-arterial infusion could have been repeated. It is also our impression that earlier institution of treatment would yield better results. Fluids would probably be effective in smaller quantities and for longer periods if introduced arterially while arterial outflow is still retarded. One should also bear in mind that the seriousness of the resultant pressure is partly determined by the degree of drop in relation to the level of accustomed pressure.[4] If treatment is instituted before the advanced state of shock as seen in most of our cases, the presence of a definite femoral pulse may also make the more simple method of femoral puncture possible.

Retrograde flow to the medullary and coronary vessels has been demonstrated to occur in intra-arterial infusions.[17,20] This phenomenon probably accounts for the respiratory stimulation which occurred frequently, the decrease of pain in two cases, and the electrocardiographic improvement in one case. Failure to elevate the arterial pressure in four cases may well be due to the advent of the irreversible stage because of the duration of shock. Following arterial infusion, one of our patients developed acute hepatomegaly without apparent cervical venous distention or increased pulmonary congestion. This development may be comparable to the hepatic congestion due to increased portal resistance shown to occur in irreversible shock.[21]

DISCUSSION

Arterial hypotension is the only constant clinical feature of coronary shock. Congestive heart failure may or may not be present,[22-24] but its frequent presence or appearance emphasizes the limited reserve of the circulatory system under these conditions. It would seem, therefore, that the usual circumstances make the use of intravenous infusion in these cases injudicious and dangerous lest

myocardial insufficiency be increased. Overdilating the heart may further decrease the cardiac output with aggravation of shock. Intra-arterial infusion in myocardial infarction is less likely than intravenous infusion to worsen or precipitate congestive heart failure. Its applicability does not depend on the venous state, nor does it abrogate steps in correcting venous dynamics.

In coronary shock the circulatory system can receive rapidly large quantities of fluid via the arteries because of the relatively empty state of these vessels. Improved myocardial action due to increased coronary flow enables the heart to meet the load imposed by elevating arterial pressure. Elevation of left ventricular pressure is accompanied by increased left coronary inflow.[25] After myocardial ischemia or hypotension, when aortic pressure is restored, coronary flow increases over control levels.[7,26] One would expect that the increased coronary flow would also affect beneficially the ultimate extent of infarction and diminish the chance of myocardial rupture. It has already been noted that the myocardial changes produced by shock are reversible and progressively improve with convalescence.[12] Intra-arterial infusion for shock, then, is more than symptomatic treatment and offers a positive therapeutic approach.

Our results seem to justify the application of intra-arterial infusion in cases of postcoronary hypotension which have not progressed to profound shock and imminent death. Such cases would also allow time, without jeopardizing the patients, to study the sequence of changes which occur with treatment. Intra-arterial infusion itself is not new and has been successfully applied in other conditions. But although our small experience with its application in coronary shock seems encouraging, the extremely serious nature and depleted reserve of the patients call for utmost caution in its application. We would also point out that the full potentialities of the procedure in coronary shock are yet to be explored. Judicious handling requires complete familiarity with the dynamics of the circulatory derangement and readiness to cope with other complications that might arise.

CASE SUMMARIES

I. S., a 56-year-old white man, was admitted to the hospital in a state of shock five hours after coronary occlusion. The pulse was 110, the blood pressure 95/70 mm. Hg. The heart sounds were poor, the lungs clear. The liver was felt one fingerbreadth below the costal margin; the peripheral veins had collapsed. The electrocardiogram showed anteroseptal infarction.

Shock persisted despite routine treatment, and seven hours after admission the pressure was 80/60 mm. Hg. Intra-arterial infusion of plasma was instituted. Attempts at femoral artery puncture were unsuccessful, and 400 c.c. of plasma were introduced in about six minutes via brachial artery cut-down.

During the infusion, respiratory excursions increased, and the patient became more alert. Lungs remained clear. Otherwise, the blood pressure and appearance of the patient were unchanged immediately after the infusion. One hour after treatment the blood pressure had risen to 95 to 100/70 mm. Hg; the patient was less restless, not perspiring, and color was improved. The subsequent course was uneventful. He was discharged three weeks after admission and survives ten months after treatment. The blood pressure remained at 100/70 mm. Hg.

M. F., a 63-year-old white man, was admitted to the hospital in shock following coronary occlusion. The pulse was 100, the respirations 20; the blood pressure was 60/40(?) mm. Hg. The heart sounds were barely audible; the lungs were clear, the liver not palpable. The electro-

cardiogram showed posteroseptal infarction. During the succeeding twenty-eight hours, the blood pressure never rose above 60 mm. Hg systolic. The patient remained anuric and cyanotic, and he became less responsive. The veins were collaped although the liver edge became palpable one to two fingerbreadths below the costal margin.

Femoral puncture was successfully performed, and 400 c.c. of plasma were introduced in four minutes. Within the first 100 c.c. of infusion, the respiratory excursions increased, and the patient became more alert. There was no apparent distress, and at the termination of the infusion the patient otherwise appeared little changed. The systolic pressure was 55 mm. Hg. The heart sounds had become more easily audible, however, and the liver was three fingerbreadths below the costal margin; the lungs remained clear and the veins not distended. The subsequent clinical picture remained unchanged when the patient suddenly had a convulsion and ceased to breathe, after forty hours of shock and anuria, twelve hours after intra-arterial infusion.

I. B., a 78-year-old white man, was seen in shock one hour after an acute coronary occlusion. The blood pressure was 80/0 mm. Hg. The patient was admitted to the hospital more than five hours after the onset of the attack. The pulse was 100, the blood pressure 55/0 mm. Hg. The skin over the abdomen was mottled, and the nail beds were very cyanotic. He was semistuporous and restless. The lungs were clear, the heart sounds were barely audible, the liver was palpable three fingerbreadths below the costal margin; there was no peripheral edema. The electrocardiogram showed anterior wall infarction.

Two hours after admission, more than seven hours after onset of severe shock, the patient received 400 c.c. of blood via brachial artery cut-down. The 400 c.c. of blood were infused intermittently over a period of about twenty minutes because of difficulty in keeping the blood fluid. During the infusion there was an increase in respiratory excursions, but no other apparent change.

Immediately after the infusion the blood pressure was imperceptible. One hour after infusion the pressure had risen to 85/40(?) mm. Hg, but minutes after the pulse again became imperceptible. Respiration ceased after ten hours of profound shock, three hours after intra-arterial infusion.

F. G., a 53-year-old white man, was admitted to the hospital because of coronary occlusion. On admission he was in acute distress with dyspnea, orthopnea, and cyanosis. The blood pressure was 106/86 mm. Hg, the pulse 120. There were moderate cervical venous distention and crackling râles over the lower two-thirds of both lung fields. The heart sounds were muffled; the liver was down four fingerbreadths and moderately tender. The venous pressure was 168 mm. of water. The electrocardiogram showed acute posterior myocardial infarction.

The patient was digitalized and gained some relief from nasal oxygen, but the blood pressure fell rapidly to 85/65 mm. Hg, the pulse to 112. He was pale and perspiring; purplish mottling developed over the skin of the abdomen. The blood pressure continued to fall. Four hours after the apperance of severe shock the patient was given 500 c.c. of whole blood via brachial artery cut-down after unsuccessful attempts at femoral artery puncture. Just prior to the infusion, the blood pressure had become imperceptible; immediately after infusion, the blood pressure was 85/70 mm. Hg. There was no immediate increase in pulmonary congestion. An hour after infusion, the pressure had risen to 95/75 mm. Hg. The patient was no longer perspiring, the mottling had completely disappeared, and the change in facial color was suggestive of plethora. Two hours after infusion the blood pressure had risen to 100/80 mm. Hg where it remained. Five hours after the infusion dyspnea began to increase; the venous pressure was 220 mm. of water. Phlebotomy was attempted from the antecubital vein which collapsed before 100 c.c. of blood could be withdrawn. Although the arterial pressure of 100/80 mm. Hg was maintained, dyspnea and pulmonary congestion increased, and respiration ceased twelve hours after the infusion.

G. G., a 47-year-old white man, was admitted because of coronary occlusion. There was no venous distention; the heart sounds were clear. There were a few expiratory wheezes in the lungs. The liver was not palpable. The blood pressure was 175/140 mm. Hg. Three hours after admission the patient complained of increased pain in the precordium. The arterial pressure was

now 110/90 mm. Hg, the pulse 106. An intravenous infusion of 300 c.c. of plasma was administered, but the severity of shock increased and the blood pressure continued to fall. Five hours after admission the blood pressure was 100/70 mm. Hg. One thousand cubic centimeters of whole blood were administered in fifteen minutes without difficulty via brachial artery cut-down. As the infusion was started, blood pressures were audible with difficulty at less than 80 mm. Hg systolic. During the infusion there was a decrease in intensity of precordial pain and no apparent increase in pulmonary congestion. Immediately after the infusion the blood pressure was 80/70 mm. Hg; thirty minutes after infusion the blood pressure was 90/80 mm. Hg. Arterial pressure continued to rise gradually for the following three hours when it tended to level off at 110/95 mm. Hg. There was subjective improvement after the treatment although dyspnea persisted. On the fourth hospital day the liver became palpable, but there was no apparent increase in pulmonary congestion, and the arterial pressure was maintained at 110 to 115/90 mm. Hg. On the fourteenth hospital day, shortly after using the bed pan, he died suddenly.

Necropsy revealed recent infarction of the anterolateral and posterior walls, apex of the left ventricle, and interventricular septum; myocardial fibrosis, posterior one-third of interventricular septum and anterior and posterior papillary muscles of left ventricle; pulmonary emphysema.

H. I., a 67-year-old white man was hospitalized because of peripheral arteriosclerosis obliterans. He maintained a blood pressure of 150 to 170/100 mm. Hg until one week after admission when he suddenly became dyspneic, cold, and clammy, and the blood pressure was found to be 110/70 mm. Hg, the pulse 120. There were bilateral basal râles and some right upper quadrant tenderness although the liver edge was not palpable. The electrocardiogram showed acute posterior wall infarction.

Five hours after the onset of severe shock, the patient was given 500 c.c. of whole blood within eight minutes via brachial artery cut-down. Substernal pain definitely decreased during the infusion. There was no increase in pulmonary congestion, no increase in right upper quadrant pain, and the blood pressure rose to 120/80 mm. Hg. An hour after the infusion, blood pressure was 120/90 mm. Hg, color was improved, and the patient was more alert. The state of shock did not recur, and for the week following the infusion the blood pressure hovered at 120 to 140/80 to 90 mm. Hg. On the eighth day after the infusion, the patient again went into severe shock, and the arterial pressure fell to 88/50 mm. Hg. Arterial infusion was not repeated, and the patient died one hour after having been found in shock.

S. S., a 62-year-old hypertensive patient (160/100 mm. Hg), was admitted to the hospital because of coronary occlusion. On admission he appeared anxious and tense, slightly dyspneic and cyanotic, complaining of dizziness. The blood pressure was 98/84 mm. Hg, the pulse 98, the sedimentation rate 35, the white blood cell count 18,300. The electrocardiogram showed posteroseptal infarction. Three hours after admission the blood pressure had fallen to 70/0 mm. Hg, and shortly thereafter it became imperceptible, despite intravenous infusion. Two hours later, an intra-arterial infusion was started, and 500 c.c. of whole blood were given within fifteen minutes via brachial artery cut-down. During the infusion there was an increase in the rate and depth of respirations; the lungs remained clear; there was no pain. At the completion of the infusion, the cyanosis began to increase, and the patient complained of abdominal pain, mainly in the right upper quadrant. The liver on palpation had descended 2 to 3 fingerbreadths below the costal margin. About fifteen minutes after the infusion, the patient began to bear down. An electrocardiogram revealed ventricular tachycardia which rapidly became ventricular fibrillation despite direct administration of procaine amide into the heart.

B. B., a 57-year-old man, went into shock after a bowel movement on the fifth day following coronary occlusion. The patient perspired profusely, and the blood pressure, which had been 150/110 mm. Hg, became imperceptible. During the following three hours the pulse was only intermittently palpable; the heart sounds were inaudible. He was given 600 c.c. of plasma and 300 c.c. of whole blood via the brachial artery in divided quantities over a period of forty-five minutes. This was accomplished with difficulty because of the state of severe vascular collapse. During the infusion the heart sounds became audible. There was no increase in pulmonary congestion or other apparent change. The patient died one hour later.

SUMMARY

In patients with shock after coronary occlusion we have used intra-arterial infusion of blood and/or plasma which, in addition to combating shock with the least volume of fluid, has the singular action of increasing coronary flow by retrograde effect.

Eight patients in severe to profound shock of from three to twenty-eight hours following myocardial infarction were treated with intra-arterial infusion. Up to 1,000 c.c. of blood or plasma were given at a rate generally of 75 to 100 c.c. per minute. Six of these patients showed evidence of improvement as manifested by the heart sounds, respirations, degree of pain, and electrocardiogram. Elevation of blood pressure occurred in four patients in whom infusion seemed effective in enabling them to survive critical periods of shock for hours, days, or months (eight hours, eleven and fourteen days, and one survival of ten months, respectively). There was no increase in pulmonary congestion during the infusion, but one patient developed ventricular fibrillation shortly after infusion. Generally, results improved as greater facility in technique was achieved.

The results seem to justify the application of intra-arterial infusion in patients with postcoronary hypotension who have not progressed to profound shock and imminent death as those in our series.

The rationale of this treatment is discussed.

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REFERENCES

1. Billings, F. T., Jr., Kalstone, B. M., Spencer, J. L., Ball, C. O. T., and Maneely, G. R.: Prognosis of Acute Myocardial Infarction, Am. J. Med. **7**:356, 1949.
2. Mintz, S. S., and Katz, L. N.: Recent Myocardial Infarction, Arch. Int. Med. **80**:205, 1947.
3. Levine, S. C.: The Prognosis of Coronary Occlusion; Part I, Mod. Concepts Cordiovas. Dis. **11**: 1942.
4. Master, A. M., Jaffe, H. L., Dack, S., and Silver, N.: The Course of the Blood Pressure Before, During, and After Coronary Occlusion, Am. Heart J. **26**:92, 1943.
5. Rosenbaum, F. F., and Levine, S. C.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction. I. Immediate Prognosis, Arch. Int. Med. **68**:913, 1941.
6. Eckenoff, J. E., Hafkenschiel, J. H., Foltz, E. L., and Driver, R. L.: Influence of Hypotension on Coronary Blood Flow, Cardiac Work and Cardiac Efficiency, Am. J. Physiol. **152**:545, 1948.
7. Opdyke, D. P., and Forman, R. C.: Study of Coronary Flow Under Conditions of Hemorrhagic Hypotension and Shock, Am. J. Physiol. **148**:726, 1947.
8. Tennant, R., and Wiggers, C. J.: The Effect of Coronary Occlusion on Myocardial Contraction, Am. J. Physiol. **112**:351, 1935.
9. Corday, E., Bergman, H. C., Schwartz, L. L., Spritzler, R. J., and Prinzmetal, M.: Studies on the Coronary Circulation. IV. The Effect of Shock on the Heart and Its Treatment, Am. Heart J. **37**:560, 1949.
10. Prinzmetal, M., Simkin, B., Bergman, H. C., and Kruger, H. E.: Studies on the Coronary Circulation. II. The Collateral Circulation of the Normal Human Heart by Coronary Perfusion With Radioactive Erythrocytes and Glass Spheres, Am. Heart J. **33**:420, 1947.
11. Prinzmetal, M., Bergman, H. C., Kruger, H. E., Schwartz, L. L., Simkin, B., and Sobin, S. S.: Studies on the Coronary Circulation. III. Collateral Circulation of Beating Human and Dog Hearts With Coronary Occlusion, Am. Heart J. **35**:689, 1948.

12. Malory, T. B.: Systemic Pathology Consequent to Traumatic Shock, J. Mt. Sinai Hosp. **16**:137, 1949-1950.
13. Melcher, G. W., Jr., and Walcott, W. W.: Myocardial Changes Following Shock, Am. J. Physiol. **164**:832, 1951.
14. Wiggers, C. J.: Myocardial Depression in Shock; A Survey of Cardiodynamic Studies, Am. Heart J. **33**:633, 1947.
15. Corday, E., Spritzler, R., and Prinzmetal, M.: Studies on the Coronary Circulation. VII. The Remarkable Reserve Power of the Heart, Ann. Int. Med. **31**:450, 1949.
16. Boyer, N. H.: Cardiogenic Shock, New England J. Med. **230**:226, 1944.
17. Glasser, O., and Page, I. H.: Experiment Hemorrhagic Shock; A Study of Its Production and Treatment, Am. J. Physiol. **154**:297, 1948.
18. Kohlstaedt, K. G., and Page, I. H.: Hemorrhagic Hypotension and Its Treatment by Intra-arterial and Intravenous Infusion of Blood, Arch. Surg. **47**:178, 1943.
19. Page, I. H.: On Certain Aspects of the Nature and Treatment of Oligemic Shock, Am. Heart J. **38**:161, 1949.
20. Jones, P. G., Davis, J. H., Jr., Hubay, C. A., and Holden, W. D.: Physiologic Mechanisms of Intra-arterial Transfusion, Surgery **27**:189, 1950.
21. Wiggers, C. J., Opdyke, D. F., and Johnson, J. R.: Portal Pressure Gradients Under Experimental Conditions, Including Hemorrhagic Shock, Am. J. Physiol. **146**:192, 1946.
22. Agress, C. M., Rosenburg, M., Schneiderman, A., and Brotman, E. J.: Blood Volume Studies in Shock Resulting From Myocardial Infarction. I. Studies With Evans Blue Dye (T-1824), J. Clin. Investigation **29**:1267, 1950.
23. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Circulatory Dynamics in Myocardial Infarction, Arch. Int. Med. **54**:997, 1934.
24. Stead, E. A., and Ebert, R. V.: Shock Syndrome Produced by Failure of the Heart, Arch. Int. Med. **69**:369, 1942.
25. Gregg, D. E., and Shipley, R.: Augmentation of Left Coronary Inflow With Elevation of Left Ventricular Pressure and Observations on the Mechanism for Increased Coronary Inflow With Increased Cardiac Load, Am. J. Physiol. **142**:44, 1944.
26. Katz, L. N., and Lindner, E.: Quantitative Relation Between Reactive Hyperemia and the Myocardial Ischemia Which It Follows, Am. J. Physiol. **126**:283, 1939.

ISOLATED TRAUMATIC RUPTURE OF THE INTERVENTRICULAR SEPTUM DUE TO BLUNT FORCE

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PROVED cases of isolated rupture of the healthy interventricular septum due to nonpenetrating chest injury are rare. Case reports prior to 1926 do not include the results of post-mortem microscopic study of such cases and usually lack detailed information regarding the prior health of the injured person. Gore[1] stressed the need for a critical evaluation of the entire subject of cardiac injury due to trauma. Because factual data may be of value, a case is herein presented relating the clinical findings during survival of the patient for sixty-four days with autopsy confirmation.

REVIEW OF THE LITERATURE

Bright and Beck,[2] Leinhoff,[3] and Warburg[4,5] have within recent years presented reviews of the literature concerning the various types of cardiac injury due to blunt or nonpenetrating force and have included numerous examples. Although hemorrhages, fragmentations, and even small lacerations of muscle fibers in the interventricular septum are not an uncommon result of trauma, this area seems the least likely of the various myocardial structures to rupture.[6]

The literature has been reviewed for cases of isolated septal rupture without cardiac rupture in any other area. Certain case reports have not been included here because the patients were still living and autopsy confirmation of the diagnosis was thus not available[7-11] or because post-mortem findings indicated the likelihood of pre-existing disease of various types,[12-14] most notably myocardial infarction following coronary artery occlusion.[15] The twelve cases from the literature which appear to meet the criteria for isolated rupture of the healthy interventricular septum are compared in Table I.

CASE REPORT

The patient, a 21-year-old white male soldier, had been examined several times for athletic events in high school and had passed an Army induction physical examination five months before injury without abnormal findings in the heart. He had never suffered symptoms of cardiac disease and gave no history of rheumatic fever or other illness predisposing to cardiac disease.

On the night of Dec. 22, 1950, the patient fell asleep while driving, and his automobile dropped 30 feet over an embankment. He was thrown forward, striking the chest against the steering wheel, making a large concave deformity in the wheel. Upon regaining consciousness an estimated thirty minutes later, he was being transported to a physician in a near-by city. He noticed extreme

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TABLE I. COMPARATIVE FEATURES OF REPORTED CASES OF TRAUMATIC RUPTURE OF INTERVENTRICULAR SEPTUM

AUTHOR AND YEAR	AGE AND OCCUPATION OF PATIENT	MECHANISM OF INJURY	CARDIAC FINDINGS AT AUTOPSY	OTHER INJURIES	SURVIVAL TIME AFTER INJURY
Hewett,[16] 1847	5-year-old boy	Chest run over by cart	Laceration through IV septum at junction of middle and lower thirds; defect admitted fifth finger	Several ribs broken; lungs collapsed	30 min.
Giraldes,[17] 1853	12-year-old boy	Fall from housetop	Tear through upper part of muscular interventricular septum for its entire width	Fractures of mandible and both femurs; rupture of spleen	4 hr.
Hoering,[18] 1864	Soldier	Left lower thorax kicked by horse	Contusion anterior surface of heart at apex; linear tear through IV septum 2 cm. long with adherent blood clot	None described	60 hr.
Flint,[19] 1870	25-year-old laborer	Struck on left chest by board	Cardiac enlargement and dilatation; fistulous opening through lower part of IV septum, admitted end of forefinger	None described	21 mo.
Rosenthal,[20] 1883	28-year-old laborer	Chest compressed between two railway cars	Ecchymoses along A-V groove; sharp-edged crescent-shaped perforation through muscular IV septum 4 cm. long	None	8 days
Popoff,[21] 1889	Railway workman	Chest compressed between couplings of two railway cars	Ecchymoses on anterior surface of heart; in IV septum near apex a perforation freely admitted a finger	Ruptures of spleen, lungs, kidneys	15 days
McOscar and Voelcker,[22] 1897	Man	Run over by wheels of empty wagon	Transverse rupture of IV septum, complete for 1 inch anteriorly	Superficial abrasions	8 days
Gross,[23] 1901	12-year-old boy	Chest run over by vehicle	Laceration 3.8 cm. long transversely through the IV septum, extending onto but incompletely through the posterior wall of the left ventricle	Left retroperitoneal hematoma; rupture of left kidney	12 hr.
Urbach,[6] 1922	28-year-old locksmith	Chest crushed by heavy piece of iron	Subepicardial ecchymoses; tear 2 cm. long through muscular IV septum, bordered by lacerated muscle fibers	Fracture of sternum, several ribs on both sides; bilateral lung injury	Exact time not stated
Husten,[24] 1926	Cabinet maker; age at injury 23 years	Struck on left chest by kick from motor crank	Right auricle, right ventricle, and pulmonary conus widely dilated; funnel-shaped perforation of IV septum tapering toward right ventricle where the defect was 10 by 18 mm. in size	Fracture of left fourth to ninth ribs at time of accident	6 yr.
Vishegorodseva,[25] 1941	Electrician; age at injury 25 years	Struck on left chest by 16 kg. iron hammer	Enlarged heart; cone-shaped depression on left side of IV septum near apex with perforation into right ventricle 0.4 cm. in diameter	Superficial abrasions, initially (death due to influenzal pneumonia)	11 yr. 8 mo.
Soulié and associates,[26] 1946	Farmer; age at injury 25 years	Kicked in left chest by horse	Generalized cardiac hypertrophy; defect in posterior-inferior portion of IV septum 13 mm. in diameter surrounded by scar tissue and with adherent blood clot	None	5 yr. 4 mo.

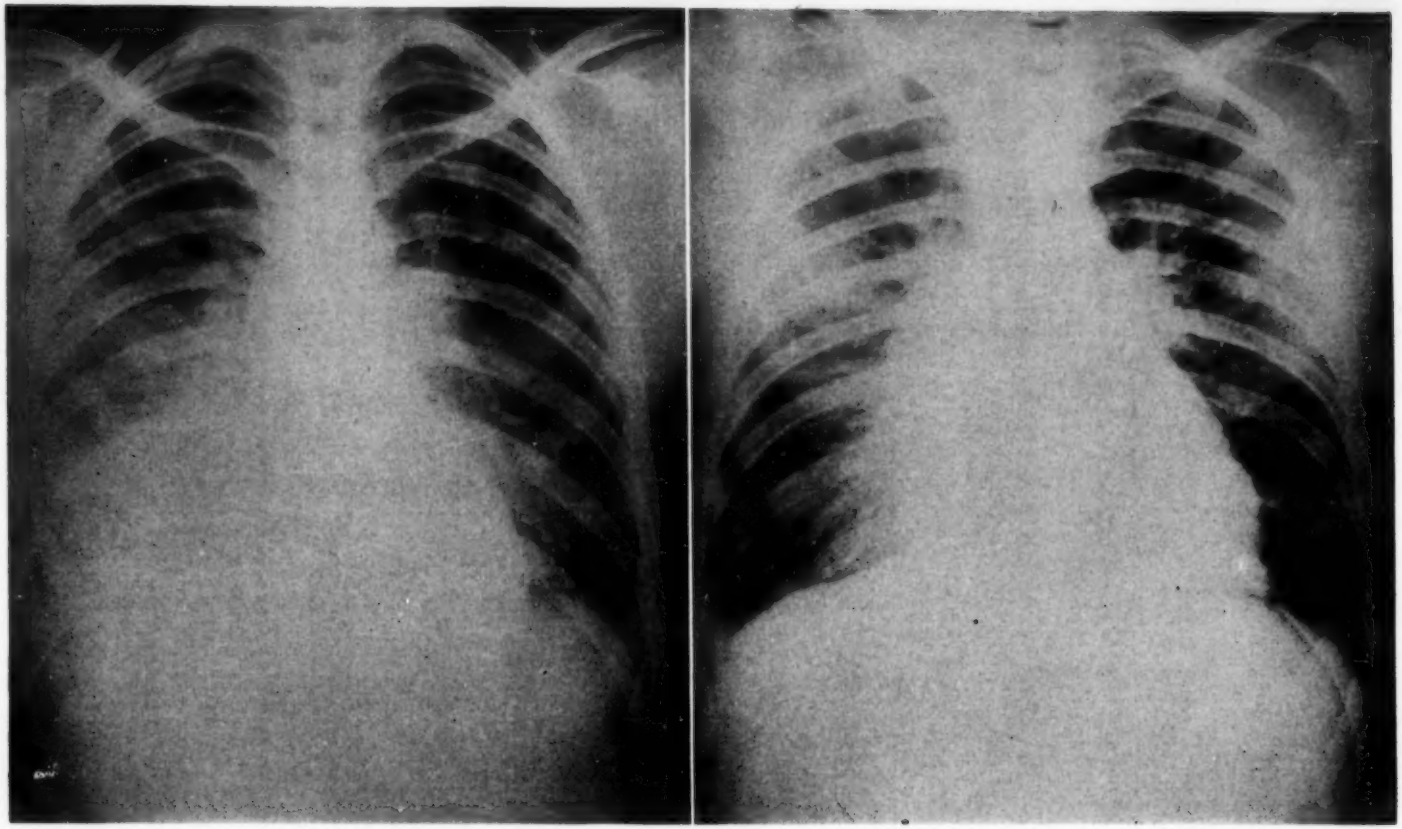
shortness of breath and pain in the right side of the chest. A roentgenogram revealed a rib fracture, and adhesive tape was applied to the chest. Auscultation was not performed. For four days he remained at home, treating himself with analgesics. Orthopnea was so severe that he had to sleep sitting in a chair. Dyspnea continued, and he frequently coughed up bright red blood. On Dec. 26, 1950, because of continuing symptoms, he entered an Army hospital.

Physical examination on the day of admission revealed a normally developed, well-nourished, 21-year-old white man, sitting upright in bed in moderate respiratory distress. The lips and face showed dusky cyanosis. Breathing was shallow at a rate of 36 per minute, with splinting of the chest especially on the right. The patient had occasional cough productive of a small amount of bright red blood. There were abrasions of the right side of the chest posteriorly. The blood pressure was 118/80 mm. Hg; the pulse was regular at 112 per minute. There was point tenderness over the fifth right rib in the anterior axillary line. Breath sounds were diminished over the right side of the chest, especially at the right base posteriorly. Tactile fremitus was absent over the right lung base. The cardiac size and configuration were within normal limits by percussion. A systolic thrill was palpable along the left sternal border at the fourth and fifth intercostal spaces. At this location were heard a harsh, loud holosystolic murmur replacing the first heart sound and a rough, early diastolic murmur of moderate intensity. The systolic murmur was transmitted to the right and left into the upper anterior chest and posteriorly to the interscapular area while the diastolic murmur was localized. Jugular and brachial venous pressures were not elevated by clinical observation. The liver and spleen were not palpable. There was no peripheral edema. The leukocyte count was 12,450 per c.mm., with a normal differential count, and the hemoglobin was 13.5 Gm. per 100 c.c. Urinalysis and cardiolipin tests were negative. Roentgenograms of the chest on admission revealed dense mottling in the entire right lung field, with thickening of the right interlobar pleural fissure and an obliteration of the right costophrenic angle by fluid. A fracture was seen involving the fifth right rib anteriorly. There was also some increase in the lung markings on the left side with some obliteration of the left costophrenic angle. The mediastinal structures were in the midline (Fig. 1,*A*). The electrocardiogram of Dec. 28, 1950, showed a deep Q wave and inverted T wave in Leads III and aV_F. Successive electrocardiograms during hospitalization revealed gradual reduction in depth of the Q wave and the development of right ventricular hypertrophy (Fig. 2).

Oxygen was administered by nasal catheter for the first twenty-four hours of hospitalization. A right thoracentesis produced 40 c.c. of serosanguineous fluid. A procaine intercostal nerve block was performed at the site of fracture with relief of pain. The maximum temperature was 100° F. on December 26 and 27, 99.2° F. on December 28, and normal thereafter. By December 30, physical examination of the left lung field showed no abnormal signs, but an area of decreased breath sounds remained at the right lung base, and the liver was palpable 4 cm. below the right costal margin. The volume of sputum decreased, but it was still blood streaked.

On Jan. 4, 1951, venous pressure was 130 mm. of water with a rise to 180 mm. on hepatic pressure; circulation time (Decholin 2 c.c.) from arm to tongue was seventeen seconds. Fluoroscopic examination of the heart in various positions showed no abnormality in shape or position and no evidence of chamber enlargement. Cardiac contractions were rapid and forceful. In an attempt to secure respiratory comfort, the patient kept the head of the bed elevated 60 degrees day and night. The exertion of walking a few steps was followed by severe dyspnea. The patient coughed occasionally, but produced little sputum, no longer blood tinged. After digitalization on January 7 to 9, he felt less dyspneic on exertion. Venous pressure decreased to 110 mm. of water, rising to 170 mm. on hepatic pressure. He then maintained fairly good subjective improvement for the ensuing week.

On January 15, the patient developed increased orthopnea and a severe cough with pain over the right fifth rib; the sputum was pink streaked, and crepitant râles were heard at both lung bases. X-ray studies showed marked pulmonary congestion bilaterally, increase in the transverse diameter of the heart, and a small amount of pleural effusion bilaterally at the lung bases. On the institution of a salt-free diet and the use of mercurial diuretics (1 c.c. intravenously at twenty-four to forty-eight hour intervals) the patient promptly improved to the degree that within ten days he was able to walk one block without dyspnea, but mild orthopnea persisted.



A. B.

Fig. 1.—*A*, Roentgenogram of the chest on Dec. 26, 1950, showing mottling in right lung field, obliteration of the right costophrenic angle by fluid, some increase in lung markings on the left side, and a heart silhouette within normal limits. The film also showed a fracture of the fifth right rib anteriorly. *B*, Roentgenogram of the chest on Feb. 19, 1951, showing increase in cardiac size in all diameters and clearing of the lung bases, but marked congestion of hilar vessels.

Two weeks later on Feb. 13, 1951, the patient somewhat suddenly lost his orthopnea and was able to lie horizontally without discomfort. During the day he complained of nausea and had diarrhea which became worse during the next twenty-four hours. The electrocardiogram

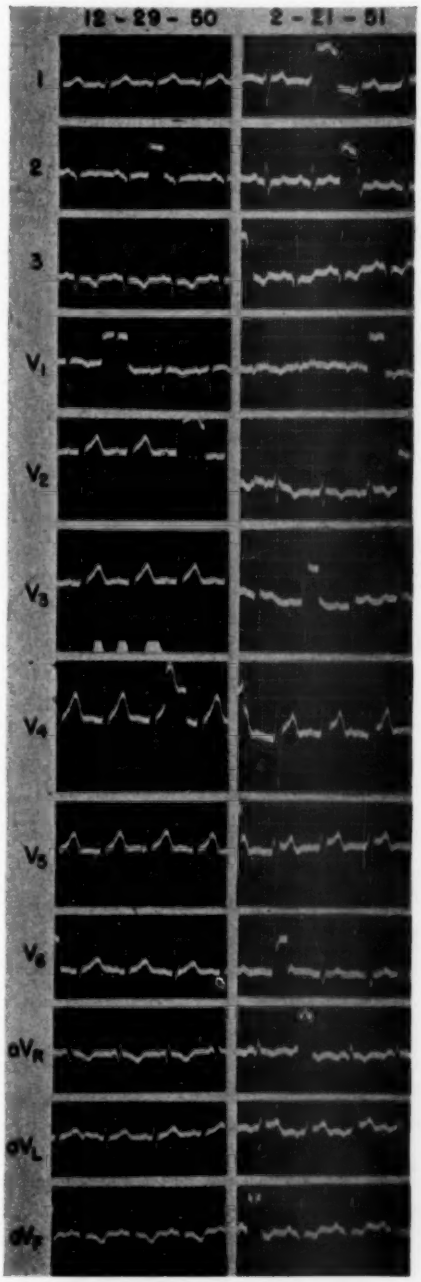


Fig. 2.—A comparison of the initial electrocardiogram of Dec. 29, 1950, which shows a Q_3T_3 pattern, with the last electrocardiogram taken on Feb. 21, 1951, which shows the pattern of right ventricular hypertrophy.

revealed frequent ventricular premature beats with long periods of coupling. Digitalis, which had been maintained at 0.2 Gm. daily, was omitted. Aqueous 5 per cent glucose solution was given intravenously to supplement an inadequate oral fluid intake to a total of 1,500 c.c. daily. Potassium chloride averaging about 2 Gm. daily was given orally or parenterally. During the ensuing week diarrhea ceased, but nausea and occasional vomiting continued and the patient took very little food. The liver was felt 8 cm. below the right costal margin, tender and with a sharp edge, but it was not pulsating although pulsations were present in the dorsal cephalic veins. Pitting edema developed in the legs and back and gradually became worse. The electrocardiogram showed fewer ventricular premature beats. Venous pressure was 250 mm. of water, and arm-to-tongue circulation time was 29 seconds. On February 19, the "direct" quantitative van den

Fig. 3.—Gross appearance of the heart as seen from the anterior view with the right ventricle opened. The area of the pericardial adhesions is seen on the anterior surface of the right ventricle. The dark area in the septum represents the perforation which communicates with the left ventricular cavity. The moderator band was cut during the process of opening the right ventricle. (Courtesy Letterman Army Hospital Photographic Laboratory, Neg. No. L-6126.)

Bergh test was 0.35 mg. per cent, the "indirect" 2.17 mg. per cent. The roentgenogram of the chest showed marked increase in cardiac size in all diameters, 25 per cent greater than normal by Ungerleider-Clark tables (Fig. 1,*B*).

On February 21, the frequent ventricular premature beats had disappeared, and digitalis medication was resumed, but with no noticeable clinical improvement. By February 23, the serum sodium content had dropped from 144 meq. per liter as previously observed to 120 meq. per liter; the serum pH was 7.52; the quantitative van den Bergh test was 2.0 mg. per cent "direct" and 7.6 "indirect"; the packed cell volume was 55 volumes per cent. Oxygen was administered by the tent method in an attempt to relieve peripheral cyanosis and marked orthopnea. Visible icterus of the skin and sclerae developed. The patient's condition during the evening of February 23 was marked by severe dyspnea at rest and by apprehension requiring sedation. The pulse was 114 per minute, the blood pressure 80/60 mm. Hg. At 7:30 A.M. on February 24, the pulse rate dropped to 60 per minute and at 8 A.M. to 40 per minute. Both lungs rapidly filled with moist râles, and the patient died at 8:15 A.M., sixty-four days after the chest injury.

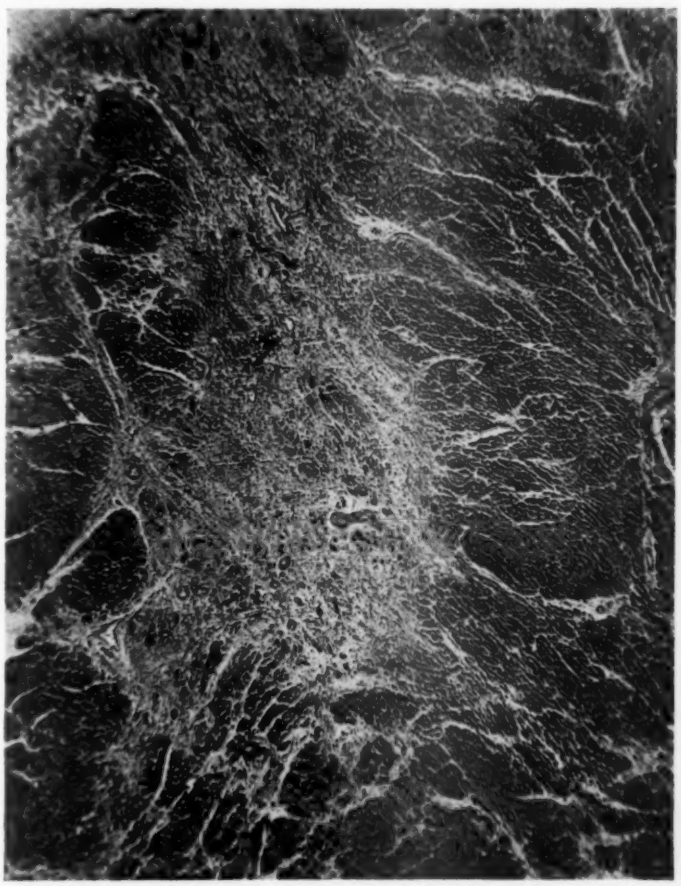


Fig. 4.—Large scar at the edge of the rupture in the muscular ventricular septum (×60). (Courtesy Letterman Army Hospital Photographic Laboratory, Neg. No. L-6126-5.)

It was evident that, whereas from the time of injury until Feb. 13, 1951, the dyspnea and orthopnea were most in evidence, after that date these symptoms were supplanted, and elevation of venous pressure, hepatomegaly, and increasing dependent edema became the most important manifestations.

Autopsy performed two hours after death revealed a greatly dilated right atrium and ventricle with distention of the entire venous system. There were ascites, hydropericardium, and bilateral hydrothorax. Healed simple fractures were found in the right fourth, fifth, and sixth ribs in the anterior axillary line. By gross and microscopic examination the lungs, liver, spleen, and kidneys showed severe chronic passive congestion.

Fig. 5.—Small scar in the muscular interventricular septum remote from the area of major rupture (×275). (Courtesy Letterman Army Hospital Photographic Laboratory, Neg. No. L-6126-6.)

The heart showed hypertrophy preponderantly of the right ventricle. There was an area of focal fibrous adhesive pericarditis 5 cm. in diameter over the anterior surface of the right ventricle. When the right ventricle was opened, a roughly triangular aperture was seen to extend through the muscular interventricular septum into the left ventricle (Fig. 3). The straight border of the defect nearest the base of the heart commenced 1.2 cm. from the anterior border of the septum at a point beneath the anterior limb of the right posterior papillary muscle and extended for a distance of 1.5 cm. in a line perpendicular to the long axis of the septum, past the apical surface of the moderator band, to end at a point 1.4 cm. from the posterior border of the septum. The border of the defect nearest the apex was 2 cm. in length and curved away from the posterior extremity of the straight border to end 0.8 cm. from the anterior border of the septum. The anterior border completing the triangle was 1 cm. long. On the left ventricular surface the straight basal border of the aperture measured 1.2 cm., the apical border 1.8 cm., and the anterior border

0.8 cm. in length. There was a band of thickened, yellowish-white endocardium 1 cm. in width extending from the anterior border of the septum, around the defect, to the posterior border of the septum. The thickened endocardium was reflected over the edges of the orifice and onto the apical surface of the moderator band. The endocardium over the trabeculae carneae of the anterior wall of the right ventricle opposite the septal defect was likewise thick and yellowish white in color. No other gross evidence of trauma to the myocardium or to the valves or membranous septum was found. The coronary arteries were soft and pliable with uniformly patent lumina throughout.

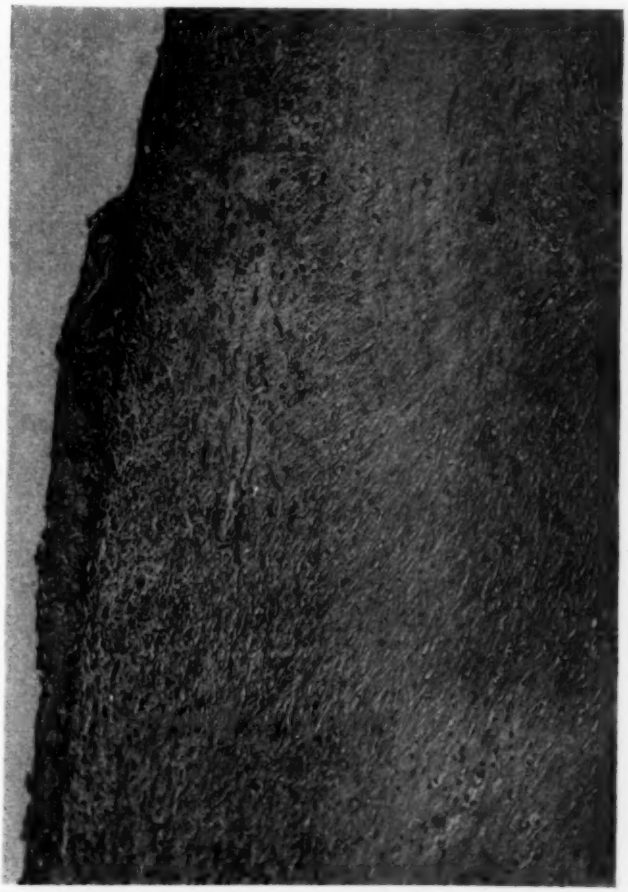


Fig. 6.—Thickened endocardium lining the edge of the rupture with adherent organizing thrombus (×125). (Courtesy Letterman Army Hospital Photographic Laboratory, Neg. No. L-6126-7.)

Microscopic sections through the edge of the septal defect disclosed large areas of young, moderately vascular scar tissue in which there was fibrous tissue proliferation, early deposition of collagen, a mild lymphocytic infiltrate, and groups of muscle cells which contained both degenerating and hypertrophic fibers with large irregularly shaped nuclei (Fig. 4). Elsewhere in the septum and the anterior walls of the left and right ventricles there were small focal areas of disruption and loss of myocardial fibers with replacement by young scar tissue, not in constant relationship with blood vessels (Fig. 5). The thickened endocardium consisted of young fibrillar scar tissue and narrow strands of collagen (Fig. 6). On the surface were occasionally seen firmly adherent fragments of organizing thrombi. There were diffuse mild interstitial edema and hydropic degeneration of myocardial fibers, the latter being most pronounced in the trabeculae carneae.

Although some small and medium-sized arteries showed endothelial proliferation, no vascular occlusion was demonstrated. The epicardium at the side of the adhesive pericarditis showed thickening with loose young connective tissue and papillary projections of the mesothelial covering. No histologic evidence of valvular damage was seen.

The bone marrow showed moderate erythroid hyperplasia in addition to congestion of the sinusoidal spaces.

DISCUSSION

Experimental work on animals[2,27,28] indicates that unusual and extreme blunt trauma is necessary to produce ruptures of the heart. The two factors apparently of greatest importance in causing heart rupture are the direction of chest compression and the phase of the cardiac cycle in which the compression is applied. A full chamber in early systole is more vulnerable if compressed over its outflow tract. Moritz and Atkins[28] pointed out that muscle fibers or groups of muscles may rupture at a point away from the area of direct contusion; the continuity of muscle bundles in the heart is such that the application of sudden tension may cause rupture a considerable distance away. This is considered the probable mechanism in our case. The importance of the steering wheel impact in compression injury of the heart has been stressed by Beck.[29]

The initial onset of symptoms of cardiac difficulty immediately following injury in the case presented suggests trauma as the etiological agent. This is particularly true when one considers the fact that the patient had previously felt himself to be in excellent health and physical examinations had shown no abnormality of the heart. The role of lung injury as against heart injury in the production of the early symptoms in the case presents a problem. The hemoptysis and a part of the dyspnea were probably due to pulmonary damage. Response to digitalization was definite, however, and demonstrated that the predominant element causing the dyspnea, orthopnea, and cyanosis was cardiac. Thereafter, the clinical course was definitely one of cardiac disease with failing compensation.

The pulmonary vascularity and congestion suggested that there was excessive pulmonary blood flow. With a low septal communication of the size noted in this case, it appears likely that the right ventricle was required to do more work in order to eject the added increment of blood from the left ventricle against an increased pressure. Relief of orthopnea in the late stage of the patient's course is considered due to the development of relative tricuspid insufficiency and fall of right ventricular pressure, thus relieving pulmonary engorgement.

The electrocardiographic pattern in our case is of interest in that the initial deep Q wave in Lead III and aV_F suggests a posterior myocardial infarction pattern whereas the laceration was entirely septal, with the anterior wall of the right ventricle showing pericardial adhesions. This pattern gradually cleared with the development of evidence for right ventricular hypertrophy, consisting of increasing right axis deviation in the standard leads, reduction in depth of the S wave in Lead V_1, decrease in the R/S ratio in Leads V_4 to V_6, increase in the height of the R wave in Lead aV_R, and increase in the amplitude of the S wave in Lead aV_L.

Differential diagnosis of the cardiac defect includes rupture of the mitral valve, its chordae tendineae, or a left ventricular papillary muscle and rupture of the interventricular septum. A diagnosis of laceration of the tricuspid valve or rupture of its chordae tendineae was not seriously entertained because it would not account for the early symptoms of dyspnea and orthopnea. Evidence against rupture of the mitral valve was the location of the thrill and murmurs at the left border of the sternum, the lack of a whirring or musical quality in the systolic murmur, and the lack of enlargement of the left atrium as seen during fluoroscopic study. Presence of a diastolic murmur in the case would seem to favor a valve laceration as the cause. Fowler and Failey,[15] however, found a diastolic murmur in three out of forty-five cases of perforation of the interventricular septum due to myocardial infarction. Selzer[30] found that early diastolic blowing murmurs were commonly noted in cases of pure congenital interventricular septal defects and questioned whether they originated in the defect or were due more probably to relative pulmonary valve insufficiency.

Rupture of a papillary muscle of the left ventricle was unlikely, primarily because of the continued survival of the patient[31] and, second, because of the lack of a bizarre quality to the systolic murmur described by Barié[32] as hollow and sonorous. The location of the murmur was not at the cardiac apex as might be expected in rupture of a papillary muscle. Rupture of a chorda tendinea of the mitral valve presents findings differing from those of the case presented; the murmur is best heard over the cardiac apex and is low toned, musical, and sonorous; it is not usually accompanied by a thrill; the electrocardiogram develops left axis deviation; fluoroscopy usually reveals enlargement and may show pulsations of the left atrium.[10,33]

The case here reported and the cases of isolated rupture of the interventricular septum reviewed conform most closely to the criteria established by Sager[34] for the diagnosis of rupture of the interventricular septum following myocardial infarction. The symptoms of traumatic rupture of the interventricular septum are shock, dyspnea, cyanosis, orthopnea, and sometimes hemoptysis and are accompanied by a brief period of fever and leukocytosis. The findings on physical examination are those of congenital interventricular septal defect: a loud, long systolic murmur, best heard at the left border of the sternum in the fourth or fifth intercostal space, a systolic thrill in the same area, perhaps a short early diastolic murmur. The course is marked by the development of left-sided heart failure and later right-sided congestive heart failure.

Gore[1] demonstrated that a history of good health up to the time of trauma, immediately followed by the first symptoms of myocardial damage, does not always provide sufficient reason for making a diagnosis of traumatic heart disease. In this case the pathological examination provides further evidence in favor of a causal relationship of the injury to the cardiac abnormality which led to death. The scarring around the septal defect, the adhesive pericarditis, and the multiple small scars remote from the major ruptures were of a histological age consistent with the duration of symptoms and were comparable with experimental traumatic lacerations of two to three months' duration as described

by Moritz and Atkins.[28] The right ventricular hypertrophy undoubtedly resulted from the increased burden of handling the blood shunted from the left ventricle under pressure. The diffuse mild myocardial edema and hydropic degeneration, the probable result of the generalized chronic passive congestion, would have contributed to myocardial failure. The poor oxygenation due to chronic passive pulmonary congestion was probably responsible for the erythrogenic response observed in the bone marrow.

Length of survival of the patient after traumatic rupture of the interventricular septum appears to depend upon two factors: the severity of injury to other parts of the body and the size of the septal perforation. The patients with shortest survival times showed extensive extracardiac injury[6,16,17,23] or very large septal perforations.[20] Four patients in the literature[19,24-26] survived longer than our patient, in fact for a matter of years. In none of these patients were there more severe extracardiac injuries than fractures of ribs, and in each of the four the perforation of the interventricular septum was less than 2 cm. in diameter.

SUMMARY

The case of a man 21 years old with traumatic rupture of the healthy interventricular septum without rupture of other structures of the heart is presented. The patient initially manifested symptoms of dyspnea, orthopnea, and hemoptysis consistent with injury to the lungs and left-sided heart failure. The later signs and symptoms were those of right ventricular enlargement and right-sided congestive heart failure. A loud systolic murmur, maximal at the left border of the sternum in the fourth and fifth intercostal spaces, was present. A systolic thrill and a soft, early diastolic murmur were also noted at the same point. The course, electrocardiographic findings, and changes in roentgenograms of the chest during survival of the patient for sixty-four days are related. Findings of the post-mortem gross and microscopic examinations are presented.

The pertinent literature is reviewed, and brief accounts are given of the twelve previously reported cases. A differential diagnosis is presented including traumatic rupture of the mitral or tricuspid valve, chordae tendineae of the mitral valve, or a left ventricular papillary muscle, and an attempt is made to identify the diagnostic features of traumatic rupture of the interventricular septum.

The length of survival of the patient after injury appears to depend upon the extent of immediate extracardiac injury and the size of the septal perforation.

REFERENCES

1. Gore, I.: The Question of Traumatic Heart Disease, Ann. Int. Med. **33**:865, 1950.
2. Bright, E. F., and Beck, C. S.: Non-penetrating Wounds of the Heart; A Clinical and Experimental Study, Am. Heart J. **10**:293, 1935.
3. Leinhoff, H. D.: Direct Non-penetrating Injuries of the Heart, Ann. Int. Med. **14**:653, 1940.
4. Warburg, E.: Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-penetrating Traumatic Injuries, London, 1938, Oxford University Press.
5. Warburg, E.: Myocardial and Pericardial Lesions Due to Non-penetrating Injury, Brit. Heart J. **2**:271, 1940.

6. Urbach, J.: Die Verletzungen des Herzens durch stumpfe Gewalt, Beitr. f. gerichth. Med. **4**:104, 1922.
7. Sigler, L. H.: Trauma of the Heart Due to Non-penetrating Chest Injuries, J. A. M. A. **119**:855, 1942.
8. Sigler, L. H.: Traumatic Injury of the Heart, AM. HEART J. **30**:459, 1945.
9. East, T.: Traumatic Rupture of the Interventricular Septum, Brit. Heart J. **7**:116, 1945.
10. Bayrd, E. D., and Gibson, S.: Traumatic Cardiac Injury in a Child With Probable Rupture of the Interventricular Septum, J. Pediat. **24**:138, 1944.
11. Anderson, R. G.: Non-penetrating Injuries of the Heart, Brit. M. J. **2**:307, 1940.
12. Kotschenreuter, A.: Ein seltener Fall von Herzverletzung, Deutsche med. Wchnschr. **34**:2222, 1908.
13. Hoffmann, A.: Herz-und Gefaesskrankheiten und Unfall, Med. Klin. **8**:1569, 1912.
14. Draper: Rupture of the Interventricular Septum of the Heart in Consequence of External Violence, Boston M. & S. J. **101**:308, 1879.
15. Fowler, N. O., Jr., and Failey, R. B., Jr.: Perforation of the Infarcted Interventricular Septum, Am. J. M. Sc. **215**:534, 1948.
16. Hewett, Prescott: Rupture of the Heart and Large Vessels, the Result of Injuries, London Med. Gazette **4** (new series): 870, 1847.
17. Giraldes: A Communication to the Society of Surgery, Arch. gén. de méd. **2**:119, 1853. (The same case is reported by Hewett, Prescott: Traumatic Rupture of the Ventricular Septum of the Heart Without any Laceration of the Pericardium, Tr. Path. Soc. Lond. **5**:101, 1853-1854).
18. Hoering: Ruptura septi Cordis, Med. Cor.-Bl. d. Wuerttemb. gerztl. Ver. **34**:76, 1864. (Abstracted in Schmidt's Jahrb. **123**:45, 1864.)
19. Flint, Austin: Diseases of the Heart, ed. 2, Philadelphia, 1870, Henry C. Lea, p. 225.
20. Rosenthal, N.: Traumatische Ruptur des Septum Ventriculorum Cordis, Berl. klin. Wchnschr. **20**:224, 1883.
21. Popoff, G. I.: Ejenedelnaia Klinitcheskaia Gazeta, Nos. 9, 10, and 11, 1888. Cited in Editorial Articles, Injuries of the Heart, Ann. Surg. **9**:338, 1889.
22. McOscar, J., and Voelcker, A.: On a Case of Traumatic Rupture of the Interventricular Septum, Tr. Path. Soc. Lond. **48**:47-48, 1897.
23. Gross, H.: Die Traumatische Ruptur des Septum Cordis, Mitt. a.d. Grenzgeb. d. Med. u. Chir. **8**:377, 1901.
24. Husten: Perforierender Defekt des Septum Ventriculorum auf traumatische Grundlage, Verhandl. d. deutsch. path. Gesellsch. **21**:249, 1926.
25. Vishegorodseva, V. D.: Report of a Case of Traumatic Injury to the Interventricular Septum of the Heart, Klin. med. **19**:119, 1941.
26. Soulié, P., DiMatteo, J., and Chiche, P.: Traumatismes précordeaux non pénétrants. La rupture septale. L'anéurysme apexien, Arch. d. mal. du coeur **39**:41, 1946.
27. Schlomka, G.: Commotio Cordis und ihre Folgen; die Einwirkung stumpfer Brustwandtraumen auf das Herz, Ergebn. d. inn. Med. u. Kinderh. **47**:1, 1934.
28. Moritz, A. R., and Atkins, J. P.: Cardiac Contusion, Arch. Path. **24**:445, 1938.
29. Beck, C. S.: Contusions of the Heart, J. A. M. A. **104**:109, 1935.
30. Selzer, A.: Defect of the Ventricular Septum, Arch. Int. Med. **84**:798, 1949.
31. Davison, S.: Spontaneous Rupture of a Papillary Muscle of the Heart, J. Mt. Sinai Hosp. **14**:94, 1947-8.
32. Barié, E.: Ruptures valvulaires du coeur, Rev. de méd., Par. **1**:309, 1881.
33. Baily, O. T., and Hickam, J. B.: Rupture of Mitral Chordae Tendineae, AM. HEART J. **28**:578, 1944.
34. Sager, R. V.: Coronary Thrombosis, Arch. Int. Med. **53**:140, 1934.

RHEUMATIC CARDITIS IN SURGICALLY REMOVED AURICULAR APPENDAGES

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WITHIN the past eighteen months commissurotomy for mitral stenosis has been performed on eleven patients at Bellevue Hospital. In the course of this operation, a small segment of left auricular appendage is removed, and the eleven segments so obtained have been submitted to the laboratory for study. The unexpected finding of evidence of rheumatic activity in the form of subendocardial Aschoff bodies in four of these patients is the subject of this report.

MATERIAL AND METHODS

The fragments of auricular appendage received constituted the distal tip of appendage which was amputated following closure of the purse-string suture through which the operator's finger was inserted. Three segments measured 2 cm. in greatest diameter; eight segments measured 1 cm. Ten specimens were fixed in Formalin and one in Zenker's fluid. All were embedded in paraffin in the usual fashion, and some five to fifteen serial sections were cut on each. Hematoxylin and eosin stain was used.

One patient died during the operative procedure, and one died twenty-two hours following the operation. Both were autopsied, and multiple sections of heart were taken for study.

All these eleven patients had been subjected to clinical study prior to operation, and, indeed, the absence of evidences of rheumatic activity had been one of the criteria for operability. A brief clinical summary and description of the histologic findings of each of the patients showing evidence of active rheumatic carditis follows.

CASE HISTORIES

CASE 1.—A 28-year-old white storekeeper and Air Force veteran had no history of rheumatic manifestations although he had had scarlet fever in childhood. He had had symptoms of cardiac insufficiency and known heart disease for one and one-half years prior to commissurotomy. The symptoms progressed rapidly over the six-month period before admission. He was observed in the hospital for six weeks before operation. Clinically he had a slightly enlarged heart with

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mitral stenosis, aortic insufficiency without left ventricular enlargement, normal sinus rhythm, no enlargement of liver or spleen, and no edema. The preoperative period was afebrile. Repeated electrocardiograms were within normal limits. Pertinent laboratory findings were as follows: hemoglobin, 15.0 Gm. (Sahli); white blood cell count 6,100 (polymorphonuclears 60, lymphocytes 38, eosinophils, 2); erythrocyte sedimentation rate (Westergren), 1 mm. per hour.

Histologic Examination.—Within the loose subendocardial connective tissue there were discrete aggregates of large mononuclear cells with abundant somewhat basophilic cytoplasm. Nuclei were large and vesicular with prominent nucleoli. Occasional multinucleated forms were seen. The cells were grouped about central masses of clumped and fibrillar eosinophilic material. The peripheral cells of one lesion extended to the endocardium, but the endothelium was intact over all lesions and no surface reaction was noted. Two to five lesions were seen in each section. There was mild diffuse thickening of subendocardial connective tissue throughout the appendage. Moderate hypertrophy of the muscle fibers was noted. No interstitial myocardial Aschoff bodies were seen (Fig. 1).

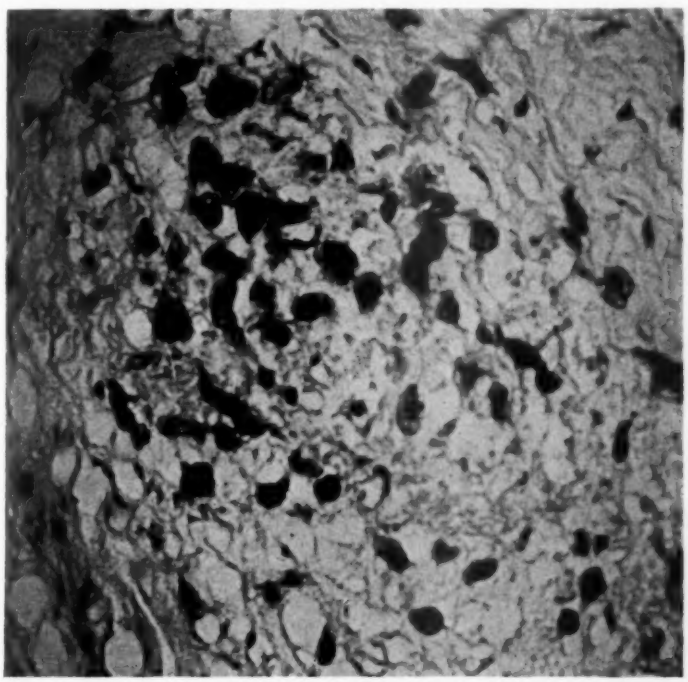

Fig. 1 (Case 1).—Typical Aschoff cells are seen in and about fragmented, fibrillar, and clumped eosinophilic material. (Hematoxylin and eosin, ×588.)

CASE 2.—A 49-year-old white Danish house painter had no history of rheumatic manifestations. The first symptoms appeared sixteen years ago. At this time he sought medical care and was told he had heart disease. The symptoms remained mild until two years ago when cardiac reserve diminished and he became incapacitated six weeks before admission. He was observed in the hospital for three weeks prior to operation. Clinically he had a moderately enlarged heart with mitral stenosis and insufficiency and no hepatosplenomegaly or edema. The patient remained afebrile. The electrocardiograms showed no prolongation of any intervals and normal sinus rhythm. Pertinent laboratory findings were as follows: The hemoglobin was 13.8 Gm. (Sahli). On admission the white blood cell count was somewhat elevated (13,500; polymorphonuclears 84, lymphocytes 16), and the erythrocyte sedimentation rate was 10 mm. per hour. Subsequently the white blood cell count fell to 7,100 (polymorphonuclears 68, lym-

phocytes 30, monocytes 2). The erythrocyte sedimentation rate after catheterization was 30 but was again 10 mm. per hour prior to operation.

Histologic Examination.—Within the subendocardial connective tissue there were focal aggregates of large polygonal cells with violet cytoplasm. The nuclei of these cells were vesicular with prominent nucleoli. Occasional multinucleated cells were seen. The cells were centered about masses of deeply eosinophilic, clumped and fibrillar material which resembled fragmented collagen. This inflammatory reaction did not extend to the luminal surface of the appendage although the endocardium bulged somewhat over each lesion. The endothelial lining was intact. There was mild diffuse thickening and increase in subendocardial connective tissue throughout the appendage. Myofibrils were moderately hypertrophied. No interstitial myocardial Aschoff bodies were seen (Fig. 2).

Fig. 2 (Case 2).—Typical Aschoff bodies in the subendocardial connective tissue. The endocardial surface is spared. (Hematoxylin and eosin, ×153.)

CASE 3.—A 25-year-old unemployed Negro man who was first known to have heart disease at the age of 10 years began to have symptoms of cardiac insufficiency at the age of 14 years. These have persisted and increased in severity to date. This patient was always difficult to control with various digitalis preparations as toxicity was a frequent complication despite close supervision. The liver was felt at the costal margin on several occasions, but he had no enlarged spleen or edema. After being observed for fourteen months in both hospital and clinic, he was readmitted to the wards and observed for thirty days prior to commissurotomy. During the hospital course he was afebrile. Repeated electrocardiograms showed no prolongation of the P-R interval and normal sinus rhythm. Pertinent laboratory findings were as follows: hemoglobin, 12.8 Gm. (Sahli); white blood cell count, 8,200 (polymorphonuclears 60, lymphocytes 40); erythrocyte sedimentation rate (Westergren) 37 mm. per hour, 25 mm. per hour.

Histologic Examination.—Within the loose subendocardial connective tissue there were frequent (four to five in each section) focal aggregates of large polygonal cells with somewhat basophilic cytoplasm and large vesicular nuclei containing prominent nucleoli. Occasional cells were

multinucleated. These cells clustered about fragmented fibrillar eosinophilic material. The inflammatory reaction did not extend to the endocardium or endothelial surface, although there was occasionally slight edema and separation of fibers in this layer with a tendency to bulge over the underlying lesion. Mild diffuse subendocardial thickening was noted. The myofibrils were moderately to markedly hypertrophied. No interstitial myocardial Aschoff bodies were seen (Figs. 3 and 4).

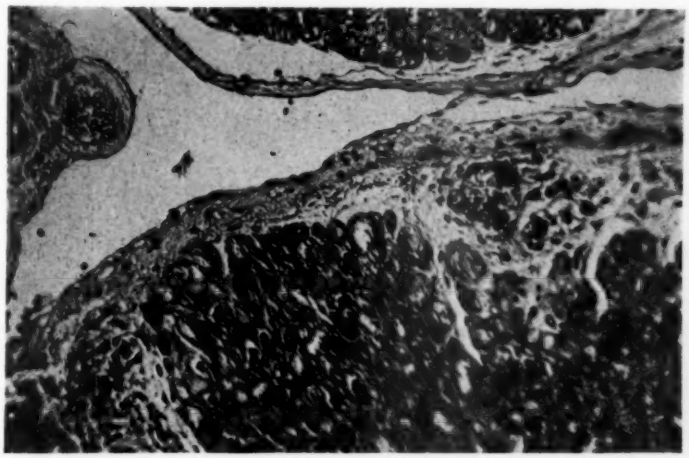

Fig. 3 (Case 3).—Aschoff bodies within the subendocardial connective tissue. The lesions spare the overlying endocardium entirely. (Hematoxylin and eosin, ×153.)

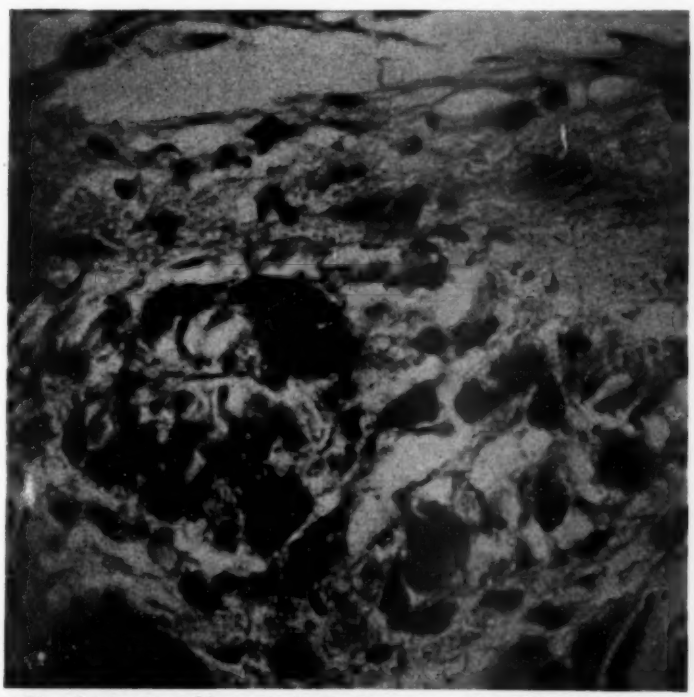

Fig. 4 (Case 3).—Aggregates of large Aschoff cells, some with multilobed nuclei and others which are multinucleated. The endothelium has been lifted off in preparation but is otherwise intact. (Hematoxylin and eosin, ×588.)

CASE 4.—A 46-year-old multiparous white housewife had had growing pains for six years following scarlet fever at the age of 6 years. She denied any other rheumatic manifestations. During the first pregnancy at the age of 25 years she was first told she had heart disease. She remained asymptomatic, however, until the age of 39 years when she went into congestive failure during a second pregnancy. Although she had had cardiac insufficiency ever since that time, there had been no real change in clinical status during the past five years. The patient was observed in the hospital for three weeks prior to operation. Clinically she had a moderately enlarged heart with mitral stenosis, regular sinus rhythm, and pulmonary congestion. There was no hepatosplenomegaly and no edema. During the preoperative period she was afebrile. Repeated electrocardiograms showed normal sinus rhythm, a P-R interval of 0.20 second and right axis deviation. Pertinent laboratory findings were as follows: hemoglobin, 12.5 Gm. (Sahli); white blood cell count, 8,400 (polymorphonuclears 79, lymphocytes 18, monocytes 2, eosinophils 1); erythrocyte sedimentation rate (Westergren) 13 mm. per hour.

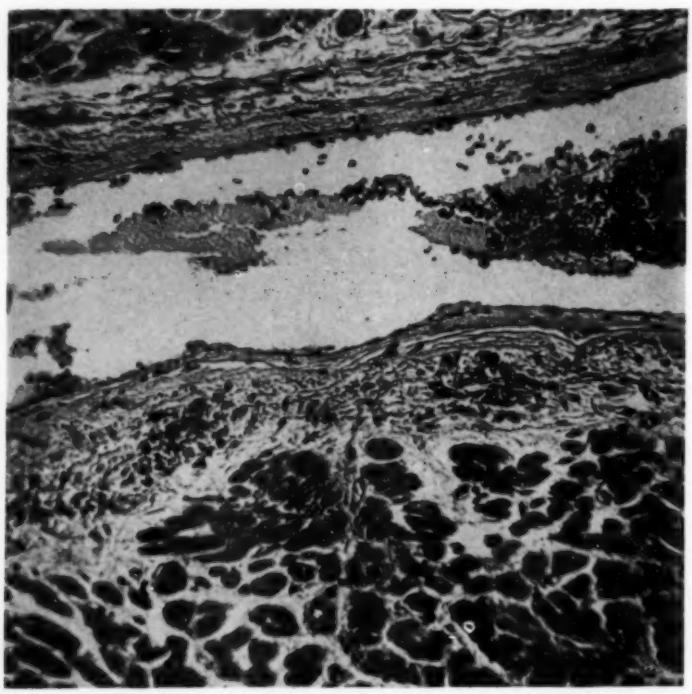

Fig. 5 (Case 4).—Small aggregates of cells in the form of typical Aschoff bodies within the subendocardial connective tissue. (Hematoxylin and eosin, ×153.)

Histologic Examination.—Within the subendocardial connective tissue small aggregates of seven to ten large and small mononuclear cells were seen clustered about fragmented, clumped, and fibrillar eosinophilic material. These cells had faintly basophilic cytoplasm and large vesicular "cart-wheel" nuclei. They did not extend to the endocardium which bulged slightly over the lesions. There was a mild diffuse increase in subendocardial connective tissue. The muscle fibers were moderately hypertrophied. There were no deeper, interstitial, myocardial Aschoff bodies (Fig. 5).

Of the seven appendages in which no Aschoff bodies were found, four contained organized thrombi. In these four, beneath the thrombi, the subendocardial connective tissue was considerably thickened and vascularized, the vessels being continuous with the newer vascular channels in the organized thrombus.

Occasional hemosiderin-laden macrophages were seen within these thrombi, and, in addition, a mild, nonspecific, diffuse infiltration of mononuclear cells and lymphocytes was observed in the endocardial connective tissue and the thrombi proper. All four patients had auricular fibrillation prior to operation and were the only ones of the group who had any arrhythmia.

Three of the patients in whom no evidence of activity was found were free of thrombi. Two of these showed mild diffuse thickening of subendocardial connective tissue. In the third, the endocardium and subendocardial connective tissue were entirely normal.

The two patients who came to necropsy were both ones in whom there were no evidences of activity in the auricular appendage. In one, multiple sections of the heart again failed to reveal active lesions. In the second a single lesion was observed at the base of the mitral valve. This consisted of a focal accumulation of large, somewhat basophilic cells, with single, multilobed, or multinucleated nuclear forms clustered about fragmented, fibrillar eosinophilic material. The lesion was consistent with an Aschoff body, but in view of the fact that no further lesions were seen in the ventricular myocardium, the auricle, or the auricular appendage, the case was classified as inactive or at best as one of questionable activity.

DISCUSSION

A review of the literature reveals no prior descriptions of Aschoff bodies in the auricular appendage. They have been repeatedly described in the auricle proper. Von Glahn's[1] study of the lesion in auricular endocarditis includes the statement that the changes observed may extend into the first portion of the appendage, but discrete Aschoff bodies in this location are not recorded. Since Aschoff bodies have been found very nearly everywhere else in the heart,[2] it would seem somewhat unusual that they have not been previously reported as occurring in the auricular appendage. The most obvious explanation for this would seem to be that the auricular appendage is not a region which is ordinarily sectioned for microscopic examination. Thus, in an exhaustive review of rheumatic auricular lesions by Gross,[3] no reference at all is made to the auricular appendage. The finding of Aschoff bodies in four of eleven cases considered clinically inactive and their frequency within each section suggests that the auricular appendage may be a favored site for their formation.

Sections of appendage are frequently taken when a thrombus is present within it. Graef, Berger, Bunim, and de la Chapelle,[4] in a report on auricular thrombosis, described evidences of rheumatic activity beneath thrombi in the appendages in seven of ten cases. In their control series of thirty rheumatic hearts without thrombi, sections of appendages were not available. These authors were of the opinion that rheumatic activity definitely predisposed to thrombus formation in the auricle proper as well as in the auricular appendage. Their criteria for activity included "residual collections of lymphocytes and, rarely, large basophilic mononuclear cells." No Aschoff bodies were described. We have felt that the chronic inflammatory reaction and the endocardial thickening and vascularization seen beneath organized thrombi might well be changes consequent to rather than a cause of thrombosis. We have limited our criteria

of activity to the one admittedly specific lesion, the Aschoff body. As to the relationship between activity and thrombosis, we can only point out that in this small series of eleven cases, four patients with activity had no thrombi, and four with thrombi had no pathologic evidence of activity. In the four patients with thrombi, auricular fibrillation had been present prior to operation, and these were the only patients of the group that had been fibrillating. Furthermore, a striking feature of the active lesions was their failure to involve the endocardial surface in the manner one might expect if they predisposed to thrombosis.

The finding of morphologic evidence of rheumatic activity in patients who clinically were presumed to be inactive serves to emphasize again that active rheumatic carditis may be difficult to appreciate clinically. However, it should be noted that no specialized techniques for the detection of rheumatic activity were employed in the medical evaluation of these patients. In retrospect, the narrow range between therapeutic and toxic doses of digitalis noted in one patient (Case 3) might have been construed as suggestive evidence of rheumatic activity as would the elevated erythrocyte sedimentation rate. The temporary elevation of the erythrocyte sedimentation rate in Case 2 was ascribed to thrombophlebitis after cardiac catheterization.

A history of well-documented rheumatic manifestations was present in only one of the four active cases here reported.

Masked rheumatic activity is a well-known phenomenon. In a group of eighty-seven rheumatic hearts studied by Gross,[3] twenty-eight were characterized by pathologic activity without clinical evidences of activity. Von Glahn[5] described a case in which myocardial Aschoff bodies were observed forty-four years after the last attack of arthritis. It is this type of experience which may explain in part the development of progressive cardiac damage in patients who show no clinical evidences of recurrence of activity or, indeed, the development of typical rheumatic heart disease in patients who have never had clinically detected rheumatic fever.

SUMMARY

Aschoff bodies, hitherto undescribed in the auricular appendage, were found in four of eleven fragments of appendage removed during commissurotomy for mitral stenosis. All of the eleven cases were considered to be clinically inactive.

ADDENDUM

Since this paper was submitted for publication, Ellis and associates, in a report of thirty-eight patients subjected to comissurotomy, have recorded the finding of Aschoff bodies in the auricular appendages of three patients (Ellis, L. B., and others: Studies in Mitral Stenosis, Arch. Int. Med. **88**:515, 1951).

REFERENCES

1. Von Glahn, W. C.: Auricular Endocarditis of Rheumatic Origin, Am. J. Path. **2**:1, 1926.
2. Clawson, B. J.: The Aschoff Nodule, Arch. Path. **8**:664, 1929.
3. Gross, L.: Lesions of the Left Auricle in Rheumatic Fever, Am. J. Path. **5**:711, 1935.
4. Graef, I., Berger, A. R., Bunim, J. J., and de la Chapelle, C. E.: Auricular Thrombosis in Rheumatic Heart Disease, Arch. Path. **24**:344, 1937.
5. Von Glahn, W. C.: The Pathology of Rheumatism, Am. J. Med. **2**:76, 1947.

Clinical Reports

RECURRENT VENTRICULAR TACHYCARDIA TREATED WITH PROCAINE AMIDE*

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SINCE Lewis'[1] first report on ventricular tachycardia, this abnormality of rhythm has been the subject of extensive investigation both as to etiology and response to various therapeutic procedures. It has been considered one of the types of cardiac arrhythmias with an unfavorable prognosis. Digitalis apparently has been responsible for bouts of ventricular tachycardia in many patients, and its connection with the onset of this abnormal rhythm has been adequately discussed by Armbrust and Levine,[2] Marvin,[3] and Scherf and Kisch.[4]

The therapy of ventricular tachycardia has been as varied as the etiological factors. Quinidine, administered either orally or intravenously, has enjoyed the greatest popularity because it has proved to be the most effective of all the agents mentioned. It is, however, a potential protoplasmic poison capable of causing cinchonism and depressant effects on the cardiac musculature and conducting system. Furthermore, some patients have exhibited idiosyncrasies to quinidine with respiratory distress, cyanosis, dizziness, cold sweats, and thrombocytopenia. Because of these hazards, physicians have always used this drug with a certain degree of apprehension and, perhaps for the same reasons, in amounts inadequate for therapeutic results.

Recently, a new drug, procaine amide, has been made available. The pharmacology and the results achieved by the use of the drug have been the subject of a recent report by Kayden and associates.[5] While the present manuscript has been in preparation, another report by Pordy and co-workers[6] has appeared describing the use of diethylaminoethanol hydrochloride in another instance of refractory ventricular tachycardia.

Because of the availability of procaine amide, we feel we can present the following clinical case report rather than a necropsy description of a patient who has suffered many bouts of ventricular tachycardia.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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*Pronestyl, E. R. Squibb & Sons, New York, N. Y.

CASE REPORT

A 60-year-old white man* was known to have had hypertension of eight years' duration with the appearance of dyspnea on effort and ankle edema during the last two years. Two months prior to admission to the hospital, he complained of chest pain during exertion and was hospitalized on Jan. 2, 1950, because of severe precordial pain which occurred at rest. Electrocardiograms were indicative of acute myocardial infarction. The patient's convalescent course was entirely uneventful, and he was discharged from the hospital two months after admission. At that time his electrocardiogram had become stabilized (Fig. 1).

A week later, increasing dyspnea on exertion and ankle edema were noted. The patient consulted his physician who placed him on an unknown maintenance amount of digitalis daily Little improvement was noted, and he was rehospitalized on April 27, 1950, for persistent heart

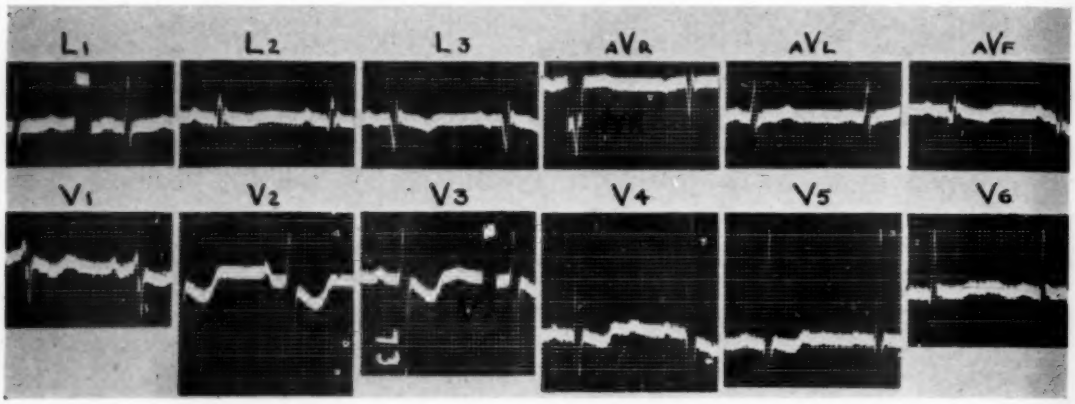

Fig. 1.—This was the patient's electrocardiogram at the time of his discharge after his first admission. The stigmas of old posterior wall myocardial infarction were present.

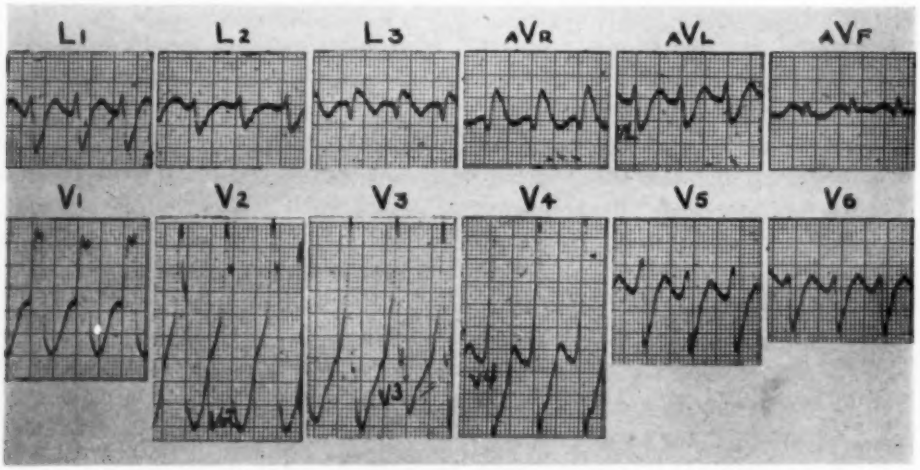

Fig. 2.—This electrocardiogram was illustrative of many episodes of ventricular tachycardia terminated by the use of procaine amide.

*A brief summary concerning the effect of procaine amide on our patient is included in the report of Kayden and associates.[5]

failure. An electrocardiogram on this admission revealed ventricular tachycardia (Fig. 2). The intravenous administration of 0.5 Gm. of procaine amide resulted in some slowing of the rate. One hour later, a second injection of 0.5 Gm. of procaine amide again slowed the rate. Fifteen minutes later, the patient vomited, and an electrocardiogram revealed a nodal rhythm with a rate of 70 beats a minute. Observation of the patient and serial electrocardiograms indicated probable recent myocardial damage. The course of the patient from this period on has been summarized in Table I. In this table we have indicated the event which we thought produced ventricular tachycardia, the measures used to prevent recurrences, and the drugs used in attempts to terminate the abnormal rhythm.

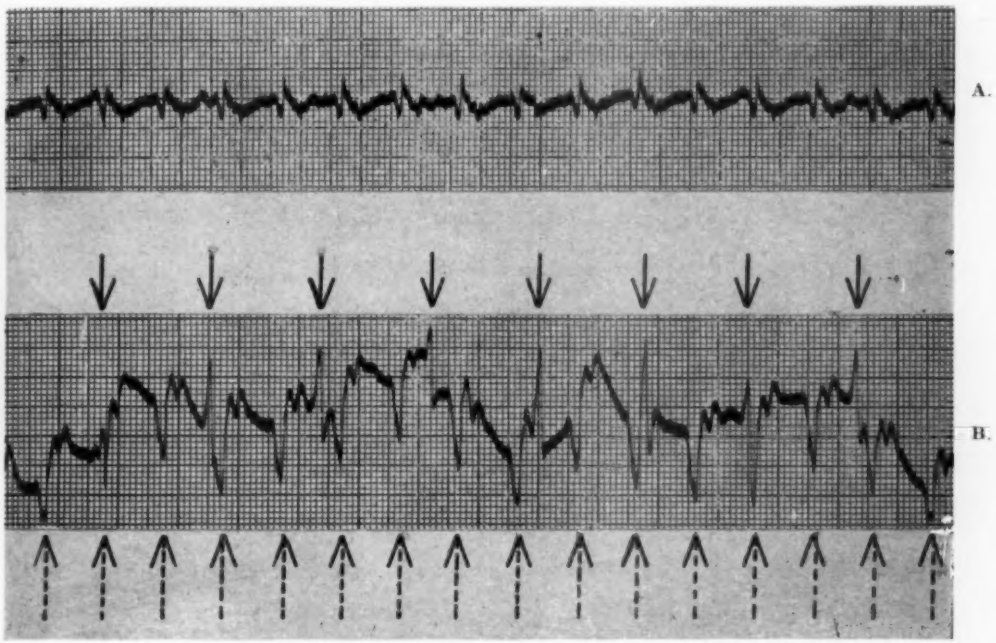

Fig. 3.—This was the patient's electrocardiogram during a bout of ventricular tachycardia. Lead aV_F (*A*) was taken simultaneously with an esophageal lead at the auricular level (*B*) to demonstrate more clearly the ventricular complexes. The solid arrow has been used to indicate the auricular complexes and the dotted arrow those of the ventricle. The esophageal lead clearly demonstrated that the auricular rate was slower than that of the ventricle. The rhythm of both auricles and ventricles was regular.

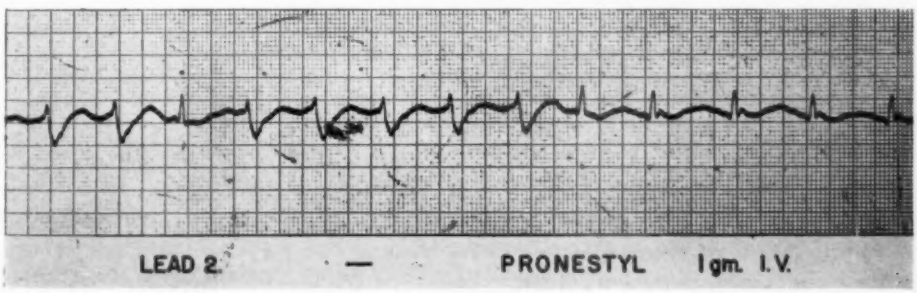

Fig. 4.—Lead II. The termination of a bout of ventricular tachycardia following the use of 1 Gm. of procaine amide intravenously was recorded. In this instance a nodal rhythm with a slower rate was established.

TABLE I. SUMMARY OF COURSE OF PATIENT WITH RECURRENT VENTRICULAR TACHYCARDIA OVER A SIX-MONTH PERIOD

DATE	PRECIPITATING EVENT	DRUG AND DOSAGE	RESULTS AND REMARKS
5/ 2/50	Strained at stool	0.4 Gm. procaine amide I.V.	Prompt reversion to regular sinus rhythm
6/11/50	Digitalization (digoxin)	0.8 Gm. quinidine sulfate orally over a 24-hour period as prophylaxis prior to digitalization	
		1.75 Gm. procaine amide orally over a 6-hour period	Regular sinus rhythm was restored
7/14/50	Digitalization (digoxin)	0.2 Gm. procaine amide I.V. followed by	Ineffective
		0.5 Gm. procaine amide I.V.	Ineffective; question as to whether ECG indicated ventricular or supraventricular tachycardia
7/15/50		0.3 Gm. quinidine sulfate orally every 2 hours for a total of 3.6 Gm.	Ineffective
		Lanatoside C I.V. 0.8 mg. followed by digoxin orally	Ineffective
7/17/50		5.4 Gm. quinidine sulfate orally in a 30-hour period	Ineffective
7/19/50		2.0 Gm. procaine amide orally	Ineffective; used again since esophageal lead (Fig. 3) unequivocally demonstrated ventricular tachycardia
		0.4 Gm. procaine amide I.V.	Ineffective
		0.5 Gm. procaine amide I.V.	Effective when administered 2½ hours after 0.4 Gm. dose; patient placed on drug, 0.5 Gm. orally, every 4 hours for prophylaxis
9/ 4/50	Digitalization (gitalin)	0.5 Gm. procaine amide I.V.	Ineffective (Note that the bout of arrhythmia occurred despite oral prophylaxis
		1.0 Gm. procaine amide I.V.	Effective with procaine amide since 7/19/50.)
9/ 7/50	Unknown	1.5 Gm. procaine amide I.V.	Effective; maintained on 0.5 Gm. orally every 6 hours
10/16/50	Digitalization (digoxin)	1.5 Gm. procaine amide I.V.	Effective (Note that the arrhythmia occurred again despite oral prophylaxis with procaine amide. Prophylaxis was continued.)
10/18/50	Strained at stool	1.0 Gm. procaine amide I.V.	Effective; oral prophylaxis discontinued
10/22/50	Unknown	1.0 Gm. procaine amide I.V.	Effective
*10/24/50 A.M.	Unknown	1.0 Gm. procaine amide I.V.	Effective
P.M.	Unknown	1.5 Gm. procaine amide I.V.	Ineffective
		2.5 Gm. procaine amide orally	Ineffective
		1.0 Gm. procaine amide I.V.	Effective

*After this episode the patient was maintained on 6.0 Gm. of the drug orally daily for more than ten months without reappearance of the arrhythmia.

DISCUSSION

This patient's hospital course was characterized by recurrent episodes of ventricular tachycardia. He has survived for a period of ten months since the first episode was observed. This is remarkable since ventricular tachycardia when associated with severe coronary artery disease has had a poor prognosis. In a summary of previous reports, Strauss[7] reported forty deaths among fifty patients with underlying heart disease and ventricular tachycardia within three hours to six months after the observation of the abnormal rhythm. Ten of twenty-four patients in Armbrust and Levine's[2] series with coronary sclerosis were dead within six months after the first attack.

Of interest in our patient was the onset on two occasions of ventricular tachycardia following a Valsalva experiment produced by straining at stool. We have not noted this phenomenon reported in any previous clinical observations. The underlying mechanism causing ventricular tachycardia under such circumstances is not clear. Perhaps increased vagal activity resulting in depression of the conduction system occurred, thus allowing an irritable ectopic focus in the ventricle to establish its own rhythm. Experimentally, it has been demonstrated that combined stimulation of the vagus and accelerator nerves of the heart will produce ventricular tachycardia. An alternative explanation has been advanced, namely, that with the increased intrathoracic pressure produced by straining, there was diminution in coronary blood flow with myocardial ischemia.

The other factor which precipitated the onset of ventricular tachycardia in this patient was the administration of digitalis (digoxin and gitalin). A direct action on the myocardium by the glycoside and depression of the conduction system of the heart have been reported as possible causes. Davis[8] supported the latter view, stating that the normal cardiac conduction system distributed supraventricular impulses so efficiently that a uniform state of refractoriness was created which resisted the establishment of circus movements in the ventricles. This equilibrium, Davis thought, was disturbed by the use of digitalis in excessive amounts. As further confirmatory evidence, he cited the frequency of bundle branch lesions as a precursory element in cases of ventricular tachycardia. Williams and Ellis,[9] in their review of thirty-six cases of ventricular tachycardia, did not encounter instances of bundle branch block but referred to the observations of others, including those of Davis,[8] and agreed that a relationship between disturbances of conduction and ventricular tachycardia may have been more than coincidental.

Of great practical importance has been the effect of procaine amide in terminating all the episodes of ventricular tachycardia in this patient. While it has been true that large oral doses of the drug failed to halt or prevent them, except in one instance, we believe that it decreased the frequency of occurrence of the abnormal rhythm. We would like to emphasize that procaine amide was repeatedly effective when administered in adequate amounts intravenously. Apparently, the parenteral route of administration was necessary to achieve therapeutic levels. As expected, transient lowering of the blood pressure did occur in this patient when procaine amide was administered intravenously, but it did not preclude its use repeatedly. Perhaps quinidine administered intravenously, or in larger doses orally, would have been an equally effective drug.

We feel that procaine amide was the drug of choice in our patient and must be considered an immediate and valuable adjunct in the treatment of ventricular tachycardia.

SUMMARY

An unusual case of ventricular tachycardia has been presented.

1. There were ten episodes of persistent ventricular tachycardia in an individual with underlying arteriosclerotic heart disease.

2. The onset of ventricular tachycardia followed a Valsalva maneuver twice and the administration of digitalis on several occasions. The possible mechanisms responsible for the onset of the abnormal rhythm have been discussed.

3. All bouts of ventricular tachycardia were terminated following the intravenous use of procaine amide.

REFERENCES

1. Lewis, T.: Single and Successive Extrasystoles, Lancet **1**:382, 1909.
2. Armbrust, C. A., Jr., and Levine, S. A.: Paroxysmal Ventricular Tachycardia; A Study of 107 Cases, Circulation **1**:28, 1950.
3. Marvin, H. M.: Paroxysmal Ventricular Tachycardia With Alternating Complexes Due to Digitalis Intoxication, AM. HEART J. **4**:21, 1928.
4. Scherf, D., and Kisch, F.: Ventricular Tachycardia With Variform Complexes, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **2**:73, 1939.
5. Kayden, H. J., Steele, J. M., Mark, L. C., and Brodie, B. B.: The Use of Procaine Amide in Cardiac Arrhythmias, Circulation **4**:13, 1951.
6. Pordy, L., and others: Paroxysmal Ventricular Tachycardia of Prolonged Duration, Am. J. Med. **10**:254, 1951.
7. Strauss, M. B.: Paroxysmal Ventricular Tachycardia, Am. J. M. Sc. **179**:337, 1930.
8. Davis, D.: Ventricular Tachycardia; An Interpretation of the Nature of the Mechanism, AM. HEART J. **7**:725, 1932.
9. Williams, C., and Ellis, L.: Ventricular Tachycardia; An Analysis of 36 Cases, Arch. Int. Med. **71**:137, 1943.

ELECTROCARDIOGRAPHIC DIAGNOSIS OF INFARCTION OF THE INTERVENTRICULAR SEPTUM COMPLICATED BY LEFT BUNDLE BRANCH BLOCK

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SINCE the report by Wilson and associates[1] on the precordial electrocardiogram, the understandability of electrocardiography has rapidly advanced. Wilson and co-workers[2] theorized the presence of a Q over the left precordium in left bundle branch block but knew that a Q could be present in the electrocardiogram recorded from the left precordium in a case with left bundle branch block only when the septum was involved by a myocardial infarction of sufficient magnitude.

A diagnosis of this type was made ante mortem, and the author feels that such a case merits presentation.

CASE REPORT

The patient was a 46-year-old white man who gave a history of "coronary occlusion" four years previously with hospitalization for thirty days. On May 13, 1950, he noted vicelike pain in the lower substernal region, radiating to the inner aspect of the left arm. This was associated with numbness, occurred intermittently for three days, was brought on by exertion and relieved by rest. Later, pressure and cramping pain radiating to the neck and to both arms were noted. There was shortness of breath. His wife had noted pallor and sweating with the attacks. There were nausea and vomiting on the day of admission.

Physical Examination.—The blood pressure was 90/70 mm. Hg. The radial pulse was 80 and somewhat irregular. The respiratory rate was 22. Orthopnea and an ashen cyanosis of the lips and skin were present. The left heart border was percussible 1 cm. lateral to the left midclavicular line in the fifth intercostal space. The heart sounds were distant and of poor quality. Frequent premature contractions, followed by compensatory pauses, were heard. The apex rate was 90. Numerous, medium, moist râles were heard throughout both lung fields. There was dullness in the bases. Moderate abdominal distention was present. The liver, spleen, and kidneys were not palpable.

Laboratory Findings.—There were 5,820,000 red blood cells and 16,000 white blood cells; the hemoglobin was 15.2 Gm. Urinalysis revealed a pH of 5.5, a specific gravity of 1.020, negative reaction for albumin and sugar, and a few hyaline casts. The Kahn test was negative. Wintrobe sedimentation rate was 11 mm. per hour.

Electrocardiogram.—This was interpreted as showing: (1) R-ST junction displacement indicative of injury against the rule (subendocardial) at V_{1-2}; (2) probable peri-infarction block; (3) frequent premature auricular and occasional premature ventricular contractions occurring in bigeminal rhythm; (4) sinus tachycardia (Fig. 1).

Course in Hospital.—The patient was given the following treatment: quinidine sulfate, 0.2 Gm. every four hours day and night; Depo-Heparin, 300 mg. subcutaneously; an initial dose of

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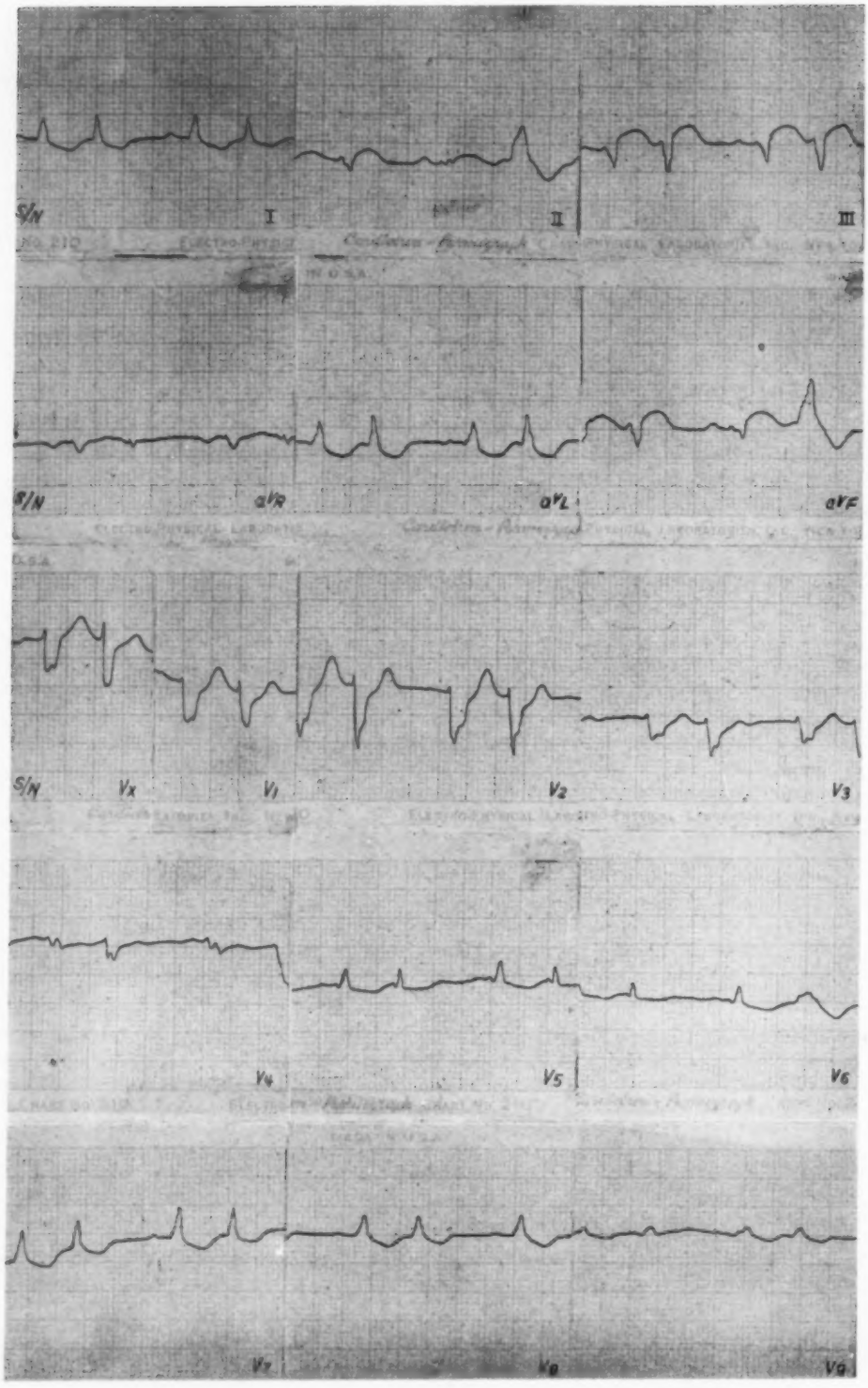

Fig. 1.—Electrocardiogram taken May 18, 1950, nine hours after admission.

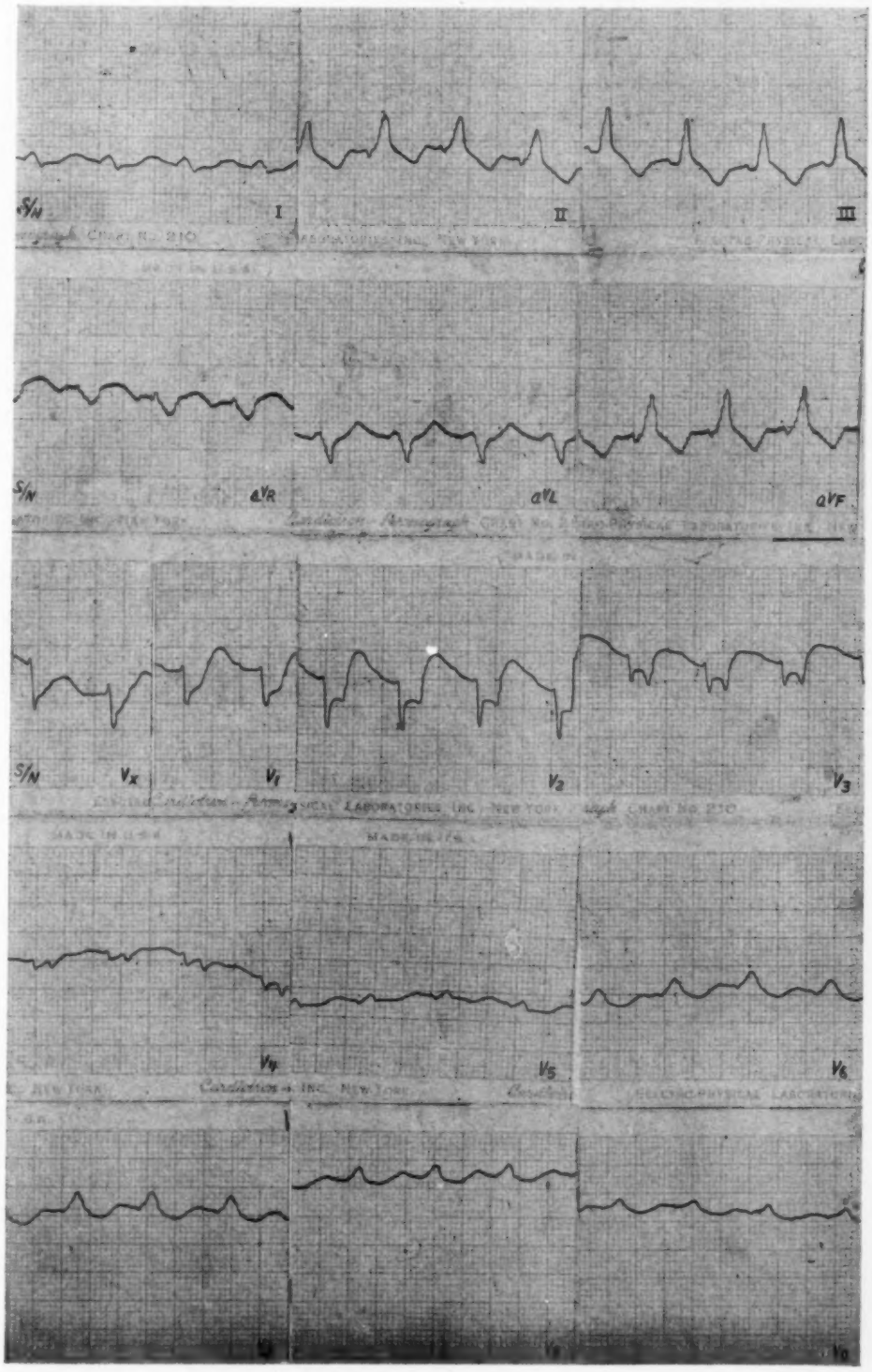

Fig. 2.—Electrocardiogram taken May 19, 1950, thirty-three hours after admission.

Dicumarol, 300 mg.; nasal oxygen, 5 L. per minute; morphine sulfate, 16 mg. hypodermically for pain and shortness of breath; a liquid diet; absolute bed rest.

The following morning the blood pressure was 94/74 mm. Hg. The frequent premature contractions continued, and the quinidine was increased to 0.2 Gm. every three hours. The pulse then became regular. Twenty-three hours after admission, the blood pressure dropped to 80/50 mm. Hg, and desoxyephedrine, 5 mg., was given hypodermically every six hours. The patient continued to require morphine. The skin was mottled, and the marked cyanosis was unrelieved by oxygen.

An electrocardiogram (Fig. 2) on the following day showed: "infarction of the interventricular septum complicated by complete left bundle branch block."

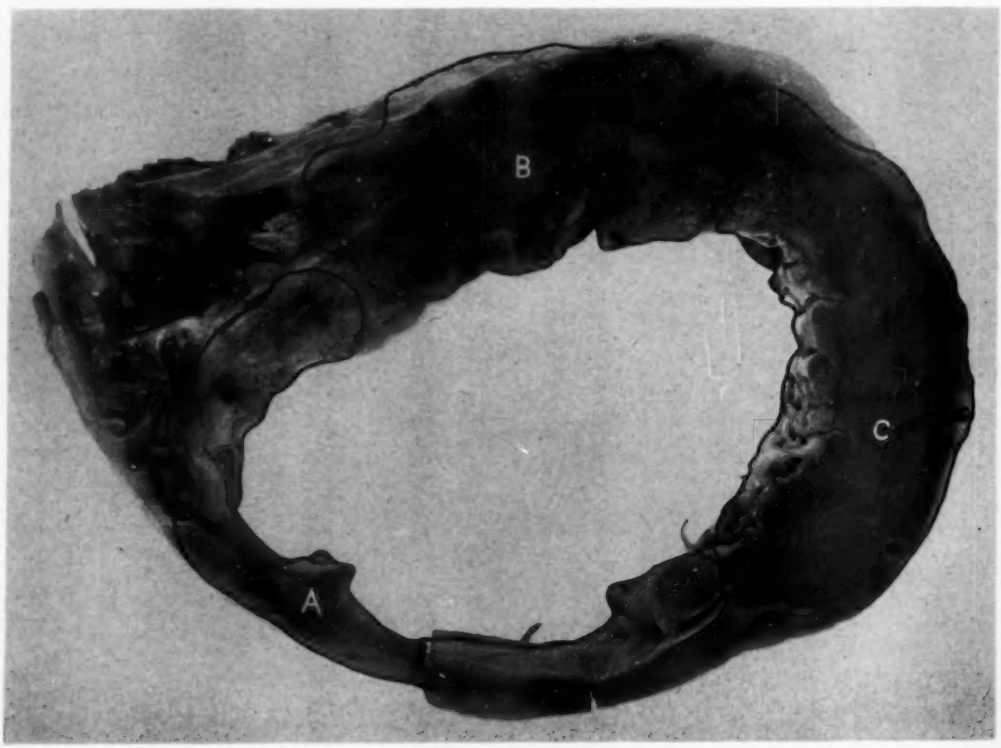

Fig. 3.—Cross section of heart showing old myocardial infarction (probably representing an "aneurysm") of the anteroseptal region (*A*), recent myocardial infarction of the posteroseptal region (*B*), and the remaining normal free wall of the left ventricle (*C*).

Oxygen therapy was changed to a Bennett mask with 95 per cent oxygen at 15 L. per minute. The cyanosis improved, and the livid mottling of the skin was relieved. The pulse slowed from 120 to 104 and the respirations from 24 to 20. At 9 P.M. on the second hospital day, the pulse was recorded as 72 and regular, and the blood pressure was 70/50 mm. Hg. Two hours later, the patient began sweating profusely. The heart once more became irregular and rapid. The patient died, fifty-one hours after admission.

The significant *necropsy* findings were confined to the heart (Figs. 3 and 4). It was apparent that there was an old infarction of the anteroseptal region of the left ventricle, probably representing aneurysmal dilatation of the left ventricle (*A*). Recent infarction involved the remaining septum and posteroseptal region (*B*). The free wall of the ventricle was normal, except for hypertrophy (*C*). Considerable passive congestion of the lungs, liver, and spleen was noted.

DISCUSSION

In the presence of left bundle branch block (Fig. 5,*A*), the activation of the left ventricle originates from the right bundle branch. From an electrode on the right precordium, an initial R is recorded as the impulse passes outward from the endocardial to the epicardial surface of the subjacent ventricular wall. From an electrode on the left precordium, an initial R is recorded as the impulse passes

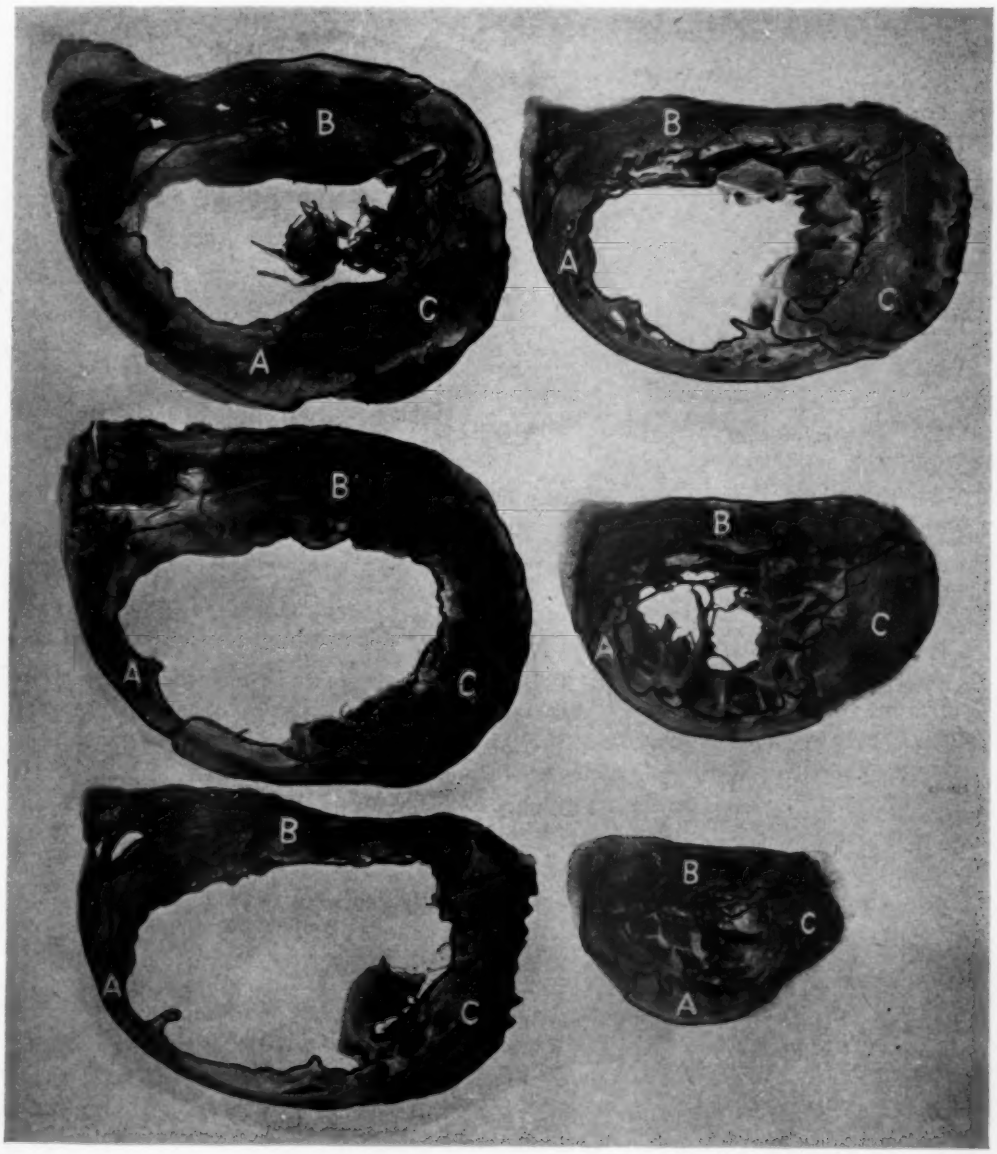

Fig. 4.—Serial sections of the heart from base (upper left) to apex (lower right) showing areas *A*, *B*, and *C* as in Fig. 3.

from the right to the left side of the septum (in a direction toward the electrode), and a Q is conspicuously absent.

When infarction of the septum is present, the impulse lies only in the free wall of the right ventricle (Fig. 5,*B*). The electrode on the right precordium sees the positive side of the approaching impulse, and the electrode on the left precordium sees the negative side of the retreating impulse. The former again records an initial R, whereas the latter now records an initial Q (at V_6, V_7, Fig. 2).

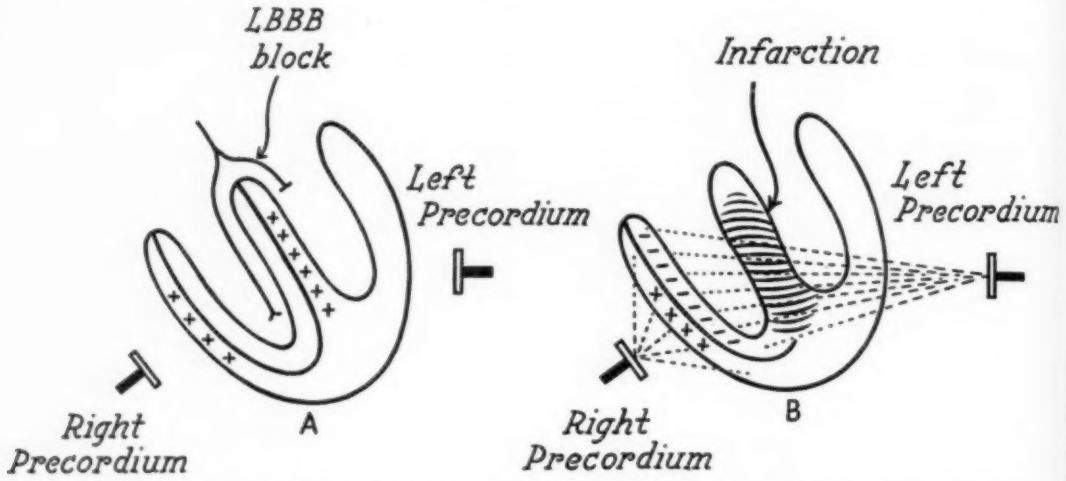

Fig. 5.—*A*, Drawing showing the activation of the right and left ventricular walls by an impulse originating in the right bundle branch of His. An electrode is represented as on the right and left precordium. *B*, Same as *A* except that an infarction is present involving the interventricular septum producing an "electrical hole" in the septum, thus causing a Q to be recorded in leads from the left precordium.

In electrocardiograms which display broad QRS intervals (0.12 plus second) of left bundle branch block form and a Q in leads from the left precordium, peri-infarction block[3] must be considered, particularly since it is considerably more frequent. Here, a late intrinsicoid deflection is seen only in unipolar leads superjacent to the infarction. In Fig. 2, the intrinsicoid deflection is late (no S wave) in all unipolar leads on the left of the transition zone, as well as at aV_F. This might be produced by peri-infarction block in the event of extensive subendocardial infarction of most of the free wall of the left ventricle. The distribution of infarction shown in Figs. 3 and 4 contradicts this possibility where zone *C* shows normal myocardium.

CONCLUSION

Differentiation of infarction complicated by peri-infarction block from infarction complicated by left bundle branch block is possible, although, at times, very difficult. Curves of left bundle branch block form with a Q in leads from the left of the transition zone usually represent the former. The author is unaware of any previous reports of examples of the latter.

Sincere appreciation is expressed to Dr. Robert H. Bayley for his helpful suggestions in the preparation of this paper and to Mrs. Bobbie Antrim for her stenographic assistance.

REFERENCES

1. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944.
2. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, Advances Int. Med. **2**:1, 1947.
3. First, Safety R., Bayley, R. H., and Bedford, D. R.: Peri-infarction Block; Electrocardiographic Abnormality Occasionally Resembling Bundle Branch Block and Local Ventricular Block of Other Types, Circulation **2**:31, 1950.

Review of Recent Advances

THE ELECTROCARDIOGRAM AND THE POSITION OF THE HEART

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ONE of the troublesome problems in the field of electrocardiography is to decide whether certain peculiarities in the tracings are due to abnormalities of the myocardium or to nothing more than an unusual position of the heart. Difficulties of this kind occur in connection with the interpretation of both limb and precordial leads and may limit the value of the records considerably. This paper is not a review of the extensive literature on the subject, but it is an attempt to point out some basic relationships between electrocardiograms and the anatomical position of the heart, to discuss some recent studies which have a bearing on the problem, and to emphasize some difficulties and unanswered questions arising from this work.

Einthoven, Fahr, and de Waart[1,2] showed that the form of the standard electrocardiogram varies with respiration or change of posture and attributed this to a change in the position of the heart. Some years later, Meek and Wilson,[3] working with dogs, reported consistent changes in the limb leads when the heart was rotated about the anteroposterior or the longitudinal axis alone and pointed out that, unless care is exercised, movement about the former axis is usually accompanied by rotation about the latter. Since the two types of rotation, so induced, act to shift the electrical axis in opposite directions, erratic and unpredicatable changes in the axis found in their early experiments were satisfactorily explained. These workers emphasized the importance of rotation of the heart on its long axis as a factor which determines the direction of the electrical axis and amply confirmed earlier studies by Groedel and Mönckeberg.[4]

It has been known for many years that standard electrocardiograms taken on normal subjects and on many patients with heart disease, often show changes if tracings are taken with the body in different positions. Thus, with the subject lying on the left side, a shift of the electrical axis to the right is usually seen, and a shift to the left may occur when the subject is lying on the right side. Alterations of this kind are particularly apt to be found in subjects with relatively

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vertical hearts, but the reverse may occur when the heart is transversely placed. In the first group it is obvious that these electrocardiographic findings are exactly the reverse of those one would expect if the heart rotated about the anteroposterior axis alone. They can only be explained by the predominant effects of accompanying rotation of the heart about the longitudinal axis. Not only may rotation of small amount about this axis cause profound changes in the appearance of the limb leads, but unfortunately movement of this kind is very difficult to estimate accurately by other means. Roentgenographic studies are of limited value in the study of rotation of this type, and many currently accepted ideas about the position of the heart are based largely, if not entirely, on electrocardiographic data.

Dieuaide,[5] in 1925, published standard electrocardiograms taken with patients lying alternately on the right and left sides. Striking differences in the tracings ordinarily caused by these changes of position were emphasized, and their absence in conditions, such as constrictive pericarditis, where the heart is fixed in the chest, was recognized and was pointed to as an aid in the diagnosis of these diseases. It is our impression that not enough attention has been paid to matters brought out by this early work, either as a guide in the diagnosis of conditions that may immobilize the heart or possibly as a tool for study of the relationships between the position of the heart and the electrocardiogram.

That change of posture does not always produce significant or consistent changes in the limb leads, even in the absence of constrictive pericarditis or allied conditions, was made clear by the studies of Nathanson[6] in 1931. Sixty individuals, including normal subjects and patients with heart disease "in whom a fixed heart was improbable," were studied in the supine, left lateral, and right lateral positions. In fifty-five of these, definite electrocardiographic alterations with change in position were found, but in the remaining five individuals (9 per cent) tracings were similar in all three positions. The most marked and constant electrocardiographic changes were found when the subjects were placed in the left lateral position. Thus, shift of the electrical axis to the right in 83 per cent, shift to the left in 6 per cent, and no significant change in 11 per cent were found in this group. In the right lateral position, on the other hand, tracings were like those obtained in the supine position in 30 per cent of the subjects, while about one-half of the remainder showed a shift of the electrical axis to the left and one-half to the right. These results seem to indicate a considerable lack of correlation between body position and the electrocardiogram in subjects without disease known to immobilize the heart. Nathanson did not, however, analyze his results on the basis of the presence or absence of cardiac abnormality, nor did he mention the types of cardiac abnormality studied, except to state that individuals with hypertensive and coronary artery disease were included in the group.

It is obvious that electrocardiographic findings in limb leads with the subject in the supine position depend to a considerable degree on the position that the heart may have in the body, and if anything, such as change in posture or forced respiration, occurs to alter this position, modifications in these leads will appear. The situation is complicated because, even in normal subjects, the amount of

rotation that can occur about three possible axes, the anteroposterior, the longitudinal, and the transverse, must depend on the motility of the mediastinal structures and the transverse and anteroposterior dimensions of the chest. Furthermore, simultaneous movement about all three axes may occur, and estimation of rotation about the latter two, except by inference from the electrocardiogram, is very difficult. When heart disease is present, abnormalities in the tracings may be exaggerated or be caused to disappear by shifts in the position of the heart. Some cardiac lesions lead to rotation particularly about the longitudinal axis, while others may prevent movement which might otherwise occur.

A recent paper by Brofman, Feil, Hellerstein, and Jones,[7] showing that changes of posture may cause the appearance or disappearance of signs of old posterior infarction in the limb leads, illustrates the difficulty that may exist in the interpretation of tracings taken from patients with known heart disease.

Wilson and co-workers,[8] in 1941, pointed out similarities often seen between the ventricular complexes of unipolar leads from the left arm and leg and those in tracings obtained from the right or the left side of the precordium in the same subject. On the basis of these observations, several positions of the heart defined entirely by electrocardiographic findings were recognized. Although it was felt by the authors that the electrocardiographic positions were in general related to the anatomical position of the heart, a necessary dependency of the former on the latter was not suggested, and caution in the interpretation of ventricular complexes of small voltage, especially those in tracings taken from points far from the heart, was advised. During the past ten years, Goldberger,[9] Myers and Klein,[10] and others, by studies which correlate the form of unipolar extremity tracings with records obtained by semidirect leads from the thorax or esophagus, have developed criteria by which it may be possible to evaluate rotation of the heart not only about the anteroposterior and longitudinal axes, but also about the transverse axis. Most of these proposals are logical, but how accurate some may be is a matter of opinion. These observations, like most other studies relating the electrocardiogram to the actual position of the heart, are supported almost entirely by electrocardiographic evidence.

The crux of the foregoing discussion, of course, revolves about the question: *To what extent can one assume that the ventricular complexes in unipolar leads reflect the potential variations existing at the surface of the heart closest to the point from which the tracing was taken?* Comparisons of direct and semidirect (precordial) leads taken during animal experiments make it clear that the QRS complexes seen in the latter closely resemble (except for size) those existing at the surface of the subjacent ventricle. Considerable evidence may be cited to indicate that the ventricular complexes in unipolar leads taken from regions quite distant from the heart are similarly determined. For example, the constancy with which QRS and T-wave changes due to posterior infarction appear in Lead V_F seems to point to a clear dependency between the potential variations of the leg and those existing on the diaphragmatic surface of the left ventricle. Myers and Klein[10] stated: "If sufficient precordial and esophageal leads are taken, a semidirect lead can be found in which the QRS-T pattern resembles that of a unipolar limb lead.

The potential variations of an extremity are governed principally by those of the surface of the heart which faces toward the limb and thus depend upon the position of the heart in the chest."

It appears likely that the foregoing views are, in general, correct, but serious doubts of their validity may arise in some abnormal tracings where deflections in the unipolar extremity leads are small. In our experience, it is not unusual to find tracings where the ventricular complexes in neither Lead aV_L nor aV_F closely resemble those seen in records taken from the right or the left side of the precordium. Furthermore, occasional tracings are seen in which the electrocardiographic position of the heart changes within a short period of time where no reason for a shift in the position of the heart is present. This is illustrated by the

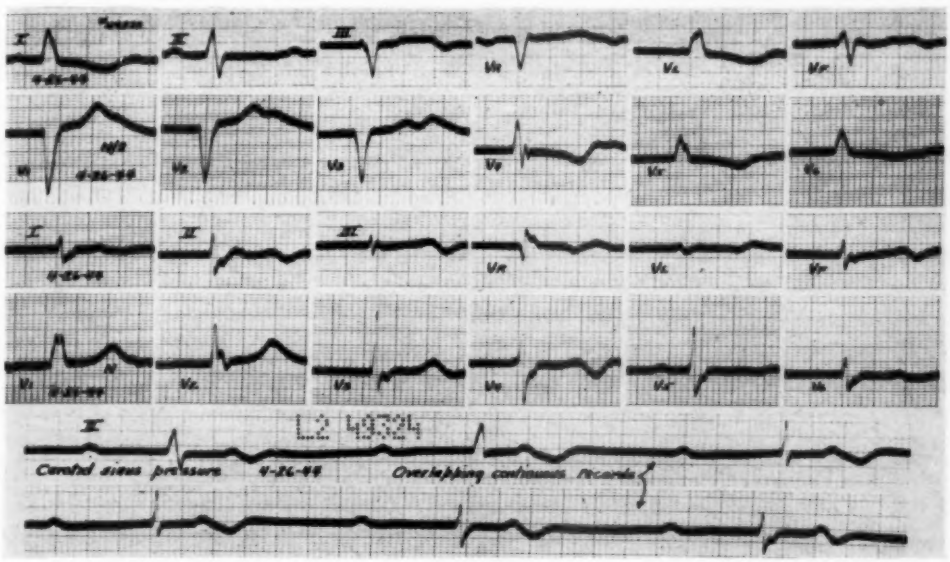

Fig. 1.—Tracings taken in rapid succession from an elderly patient with complete atrioventricular heart block. Spontaneous variation in the form of the ventricular complexes was present. Complexes of the type seen with left branch block are seen in the limb and precordial leads in the first and second rows. At this time the heart was in the horizontal position from the electrical standpoint. When complexes of the form seen in right branch block, shown in the third and fourth rows, were present, the heart was in a semivertical position. The two lower rows show a continuous strip of Lead II illustrating the change from one type of complex to the other that could be produced by carotid sinus pressure. See text.

electrocardiograms reproduced in Fig. 1. These tracings were taken in rapid sequence on a man 83 years old who had arteriosclerotic heart disease with complete atrioventricular block. Ventricular complexes resembling those seen with left bundle branch block were present part of the time, but spontaneous change to a second type of complex like those seen in right branch block occurred. It was found that carotid sinus pressure would cause a transition from the first to the second type of complex. Such a change is seen in the continuous strip of Lead II shown in the lower part of Fig. 1. Of interest here is the fact that the electrocardiographic position of the heart changed from transverse to semivertical during the transition from one type of complex to the other. This is clearly shown in the four upper sets of tracings in Fig. 1.

Studies on the spatial vectorcardiogram, particularly the work of Duchosal and Sulzer,[11] Grant and Estes,[12] and Conway, Cronvich, and Burch,[13] involve concepts that may seem hard to reconcile with the commonly accepted interpretations of unipolar leads outlined previously. The latter emphasize the importance of potential variations existing at the surface of various aspects of the heart, whereas the spatial vectorcardiogram is based on the assumption that the electrical activity *of the heart as a whole* may be represented by a series of vectors each of which indicates the direction and magnitude of the average or resultant electrical force acting within the heart at any instant. The termini of these vectors establish the figures known as vectorcardiograms. If one remembers that the methods now available for obtaining spatial vectorcardiograms are based on the proper temporal combination of figures obtained from more or less conventional surface leads in two different planes, it should be clear that the vector curves are simply a different and perhaps more informative way of expressing information usually presented in ordinary bipolar or unipolar leads. Until a more accurate and independent method for determining the direction and magnitude of voltages produced within the heart is developed, one cannot say that any basic conflict between the interpretation of vectorcardiograms and of usual surface leads exists.

These comments about spatial vectorcardiograms must not be construed as minimizing the value of work that has been done in this special field, since this is not true. As Grant and others have pointed out, all surface leads may be derived from the spatial vectorcardiogram by projection, and therefore studies which lead to its proper construction, understanding, and use may greatly simplify electrocardiographic diagnosis and teaching. Furthermore, when techniques are available for the quick and accurate estimation of these spatial curves, most current problems, concerned with peculiarities in the position of the heart, will cease to exist, because differentiation between normal and abnormal records will be made largely on the size and form of the vectorcardiograms themselves and the relations existing between various components of the spatial figures. Unusual orientation of a normal spatial complex due to a shift in the anatomical position of the heart would be readily apparent, and peculiarities in derived surface leads would be easily explained. In spite of the information to be gained by the use of vectorcardiograms, it is unlikely that these records will replace tracings of the conventional type in the near future. The many unanswered questions relative to the proper technique for obtaining spatial vectorcardiograms and the expensive and complicated apparatus required place vectorcardiography definitely in the field of research at the present time.

Gardberg and Ashman,[14] in a thoughtful paper, have tried to explain changes in the standard leads occurring with rotation of the heart, especially about the anteroposterior and longitudinal axes. On the basis of knowledge of the general course of the activation wave in the hearts of experimental animals and other data, a series of vectors in three-dimensional space representing the resultant voltages acting at a number of instants during the period of ventricular activation is described. When this series of vectors is used throughout, the character of QRS complexes that may be expected to occur in the standard leads with the

heart in various positions about the anteroposterior and long axes is clearly shown in Figs. 9 through 12 of their paper. Effects of movement of the heart about the transverse axis are also discussed briefly, and in a subsequent paper by Ashman[15] the electrocardiographic changes due to rotation of this type are considered in greater detail. Referring again to the figures published by Gardberg and Ashman, one is surprised by the large amount of rotation of the heart about the longitudinal axis which the authors believe may occur normally. This is particularly striking in their Fig. 12, which illustrates marked clockwise rotation about this axis. Here, some forces, arising primarily in the free wall of the left ventricle, are so greatly altered in direction that their projections on the frontal plane point from left to right rather than in the opposite direction. If this situation exists in the normal subject, it may occur to an even greater degree in patients with right ventricular hypertrophy or dilatation. Kossmann, Berger, Brumlik, and Briller[16] have indeed suggested that right axis deviation in the limb leads and large R waves found in precordial tracings taken from the right side of the precordium in individuals with marked hypertrophy of the right ventricle are rarely due to the enlarged right ventricle but to marked clockwise rotation of these hearts about the longitudinal axis and "almost complete reversal of the electrical fields of the two ventricles." This work challenges some of the generally accepted ideas relating to interpretation of precordial leads. This is particularly true since it is based largely on results of intracardiac electrocardiographic studies which appear to indicate, among other things, that electrical forces across the free wall of the right ventricle, even when it is hypertrophied, may be small. R waves of nearly the same size and with peaks occurring simultaneously, or nearly so, have been found in tracings obtained from the cavity of the right ventricle and from the chest wall as close as possible to the location of the intracavitary electrode by Kossmann[16] and others. This suggests, of course, that the R waves in question are due largely to forces passing from left to right through the interventricular septum. Rosenman[17] emphasized this fact and quite correctly pointed out that activation of the free wall of the right ventricle may occur during the downstroke of the R wave (the intrinsicoid deflection). Wilson and co-workers[18] discussed this matter earlier and showed why the end of the intrinsicoid deflection rather than its beginning (peak of R wave) must signal the arrival of the activation wave at the epicardial surface of the ventricle beneath the electrode.

Before these matters are considered further, some other perplexing problems relating to the interpretation of precordial leads must be mentioned. In the majority of subjects with normal hearts and patients with heart disease, the usual sites for placement of the exploring electrode are considered satisfactory, since the first two or three overlie the right ventricle and those located farther to the left are relatively close to the left ventricle. Furthermore, a line connecting the stations on the chest crosses the plane of the interventricular septum in a nearly perpendicular fashion so that the transitional zone is a narrow one. When peculiarities in the ventricular complexes in usual multiple precordial electrocardiograms, such as broadening of the transitional zone, displacement of this region to the right or left, or failure to obtain tracings of the left (or right) ventricular type, are observed, one naturally suspects an unusual position of the heart,

but reliable evidence from other sources to confirm such a view may be scanty or absent. Additional tracings taken at higher or lower levels or farther to the right or left than usual may help to explain peculiarities in the routine multiple precordial leads, and such additional studies should be obtained if it is possible. It has been suggested that the usual sites for location of the exploring electrode be altered to conform with the anatomical position of the heart in instances where the latter is suspected or is known to be unusual. At the moment such a policy would appear to be unwise, since it would add another variable to a technique which is already sufficiently complicated.

In the interpretation of precordial leads, it is generally assumed that the subendocardial tissues become electrically active very early and that the QRS complex is largely due to forces that pass in a simple radial fashion from the endocardial to the epicardial surfaces of the ventricles. The interventricular septum is believed to be activated from both sides, although considerable evidence suggests that in most human subjects with normal intraventricular conduction activation starts somewhat earlier on the left side than it does on the right. An upward deflection of the QRS complex is considered to indicate predominance of electrical forces passing toward the exploring electrode, while a downward deflection suggests that those moving away from the electrode dominate. Used with some reservations, these concepts have been of great value in the explanation of changes in the QRS complex in bundle branch block, myocardial infarction, hypertrophy, and some other conditions. Nevertheless, some findings in precordial tracings are hard to understand if one assumes the simple type of spread of the activation wave outlined.

In many normal precordial electrocardiograms, in some showing changes due to left ventricular hypertrophy, and in most records with complete left bundle branch block, S waves in tracings from the right side of the precordium are considerably larger than are the R waves in tracings from the left side. This finding is particularly striking and common in the latter group of records, and it is rather difficult to explain. One might expect the opposite situation to exist, since S waves seen in tracings obtained from the right side of the precordium presumably originate from regions of the heart some distance away from the exploring electrode, whereas the R waves in records from points over the left precordium must arise to a large extent in the free wall of the left ventricle, which is relatively close to the electrode. The difficulty here may be resolved if one assumes that the activation wave does not always travel directly outward from the endocardial to the epicardial surface of the ventricle but may spread tangentially rather than radially over parts of the ventricle. Proof for this idea is lacking, and it must be admitted that a departure from the concept of purely radial spread introduces complications to the interpretation of precordial leads.

Little attention has been paid to the muscle bundles, known to exist in the ventricles, as important factors in determining the spread of the activation wave over these chambers, but, if one considers tangential spread as a possibility, these anatomical units may play an important role. Robb and Robb,[19] a number of years ago, suggested that the activation wave may follow the course of the muscle

spirals, but no clear evidence supporting this view has been presented, and most workers have considered the ventricles to behave as a syncytium from the electrical standpoint. Recent studies which suggest that the free wall of the right ventricle, even when it is hypertrophied, contributes very small voltages during activation should be reviewed with the possibility of tangential spread of the electrical wave in mind. Close similarities in tracings obtained by a lead from the cavity of the right ventricle and one on the precordium as close as possible to the intracavitary electrode suggest that the impulse may not pass in a simple radial fashion through the free wall of the right ventricle and that tangential spread may exist. Further speculation regarding these basic matters is hardly worth while, but careful experiments, designed to answer the questions raised, are clearly needed.

Returning to the suggestion of Kossmann and co-workers[16] that signs of right ventricular enlargement in both limb and precordial leads may be due to marked clockwise rotation of the heart about its long axis, we wish to point out one fact which argues against their proposal. Right ventricular enlargement often occurs with right bundle branch block, and, under these circumstances, large, late R waves are regularly found in tracings from the right side of the precordium, including records obtained from points 3 and 4 on the right side of the chest (V_{3R} and V_{4R}). Any argument that the large, late R waves arise in the left ventricle here is clearly untenable.

McGregor[20] has recently reported that electrocardiograms taken from the surface of the heart during operations on patients with the tetralogy of Fallot show relatively small R waves and large S waves in the tracings taken with the exploring electrode in close proximity to the right ventricle and R waves that dominate the QRS complex in the records taken close to the left ventricle. These observations appear to support the view that large R waves found in tracings taken from the right side of the precordium in patients with right ventricular hypertrophy may arise from the left ventricle of a markedly rotated heart and thus support the suggestion of Kossmann and co-workers that clockwise rotation of the heart about the long axis and not hypertrophy of the right ventricle produces the large R waves in question. In these studies, however, the pericardium was not opened as a rule, and the part of the right ventricle lying nearest to the exploring electrode was probably somewhat uncertain. It would not be surprising to obtain tracings in which a small R wave and large S wave appear if the electrode were placed close to the trabeculated area of the right ventricle, and further studies with wider exploration of the hypertrophied right ventricle and more exact localization of the exploring electrode on this chamber must be carried out. If it is found that the hypertrophied right ventricle does not produce the large R waves found in records from the right side of the precordium, the reasons for its apparent lack of electrical activity must be determined. In this connection, the possibility of tangential spread of the activation wave rather than primarily radial penetration through the free wall of this chamber must be investigated.

SUMMARY

The profound effects that rotation of the heart, particularly about the longitudinal axis, have on the mean electrical axis, as seen in limb leads, are emphasized, and some of the experimental and clinical studies that bear on this matter are discussed. The advantages that spatial vectorcardiograms may have in the evaluation of electrocardiographic changes due solely to an unusual position of the heart are pointed out, but, for a number of practical reasons, it is felt that such records will not be very useful in the solution of these or similar problems in the near future.

Peculiarities in the form of tracings from the precordium due entirely to an unusual position of the heart are mentioned, but it is considered unwise (except for purposes of investigation) to recommend a change from the conventional sites for multiple precordial leads because of the suspicion that the heart may be placed in an unusual fashion.

The suggestion of Kossmann and co-workers that signs suggesting right ventricular enlargement in both standard and precordial leads may arise as a result of marked clockwise rotation of the heart about the long axis is discussed, and some evidence for and against this view is presented. Since concepts basic in the interpretation of precordial leads are involved in this problem, the need for further studies to decide the matter is emphasized. It is pointed out that tangential rather than purely radial spread of the activation wave over the ventricles may explain some of the difficulties encountered in interpretation of precordial leads, particularly when right ventricular enlargement or left bundle branch block is present.

REFERENCES

1. Einthoven, W., Fahr, G., and de Waart, A.: On the Direction and Manifest Size of the Variations of Potential in the Human Heart and on the Influence of the Position of the Heart on the Form of the Electrocardiogram, Pflüger's Arch. f. d. ges. Physiol. **150**: 275, 1913.
2. *Ibid.*, translated into English by Hoff, H. E., and Sekelj, P., Am. Heart J. **40**:163, 1950.
3. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the QRS Complex of the Electrocardiogram, Arch. Int. Med. **36**:614, 1925.
4. Groedel, T., and Mönckeberg, J. G.: Ein Fall von Kongenitaler Pulmonalstenose und die sich daraus ergebenden Schlüsse für die Initialzacke des Electrokardiogrammes, Zentralbl. f. Herz- u. Gefässkr. **5**:2, 1913.
5. Dieuaide, F. R.: The Electrocardiogram as an Aid in the Diagnosis of Adhesive Pericardial Mediastinitis, Arch. Int. Med. **35**:362, 1925.
6. Nathanson, M. H.: Electrocardiographic Study of Movements of the Heart With Change of Posture, Proc. Soc. Exper. Biol. & Med. **28**:766, 1931.
7. Brofman, B. L., Feil, H., Hellerstein, H. K., and Jones, A. M.: Postural Electrocardiographic Changes in Healed Myocardial Infarction, Circulation **3**:752, 1951.
8. Wilson, F. N., Johnston, F. D., Cotrim, N., and Rosenbaum, F. F.: Relations Between the Potential Variations of the Ventricular Surfaces and the Form of the Ventricular Electrocardiogram in Leads From the Precordium and the Extremities, Tr. A. Am. Physicians **56**:258, 1941.
9. Goldberger, E.: Unipolar Lead Electrocardiography, ed. 2, Philadelphia, 1949, Lea & Febiger.
10. Myers, G. B., and Klein, H. A.: The Relation of Unipolar Limb Leads to Precordial and Esophageal Leads, Am. Heart J. **35**:727, 1948.
11. Duchosal, P. W., and Sulzer, R.: La Vectocardiographie, Bâle, 1949, S. Karger.
12. Grant, R. P., and Estes, E. H., Jr.: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Company.

13. Conway, J. P., Cronvich, J. A., and Burch, G. E.: Observations on the Spatial Vectorcardiogram in Man, AM. HEART J. **38**:537, 1949.
14. Gardberg, M., and Ashman, R.: The QRS Complex of the Electrocardiogram, Arch. Int. Med. **72**:210, 1943.
15. Ashman, R.: Estimation of the Heart Position From the QRS Complex of the Electrocardiogram, Arch. inst. cardiol. México **16**:139, 1946.
16. Kossmann, C. E., Berger, A. R., Brumlik, J., and Briller, S. A.: An Analysis of Causes of Right Axis Deviation Based Partly on Endocardial Potentials of the Hypertrophied Right Ventricle, AM. HEART J. **35**:309, 1948.
17. Rosenman, R. H.: Observations on the Genesis of the Electrocardiogram, AM. HEART J. **40**:522, 1950.
18. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretations of the Ventricular Complex of the Electrocardiogram, Advances Int. Med. **2**:1, 1947.
19. Robb, J. S., and Robb, R. C.: The Normal Heart, Anatomy and Physiology of the Structural Units, AM. HEART J. **23**:455, 1942.
20. McGregor, M.: The Genesis of the Electrocardiogram of Right Ventricular Hypertrophy, Brit. Heart J. **12**:351, 1950.

Book Reviews

STUDIES OF UNDERNUTRITION, WUPPERTAL, 1946-9. By members of the Department of Experimental Medicine, Cambridge, and associated workers. Medical Research Council Special Report No. 275. London, 1951, His Majesty's Stationery Office, 404 pages with 62 plates. Price 12s. 6d.

This report describes, for the most part, the physiological status of those citizens of Wuppertal, just outside the Ruhr Valley in a much bombed area, who, in the years following June, 1946, applied for extra rations because of excessive loss of weight or the development of famine edema; their average age was 52 years, and they had lost about 20 per cent of their prewar weight, mainly in the last few months before the commencement of the investigation. Specific vitamin deficiencies were not observed, and the study is perhaps of especial interest because the nutritional situation was not very different from that which might be encountered in underprivileged families in Canada or the United States.

The most important section of the report, by Professor R. A. McCance, deals with nutritional edema; a very comprehensive review precedes the account of the actual findings. The conclusion is that consumption of intracellular fat and protein leads to great absolute and relative enlargement of the extracellular fluid space, an enlargement of which only a fraction is attributable to the obviously edematous regions, mainly in the lower limbs. Depletion of plasma protein and posture may be contributing factors; vitamin deficiencies, endocrine imbalance, and hepatic or renal failure seem to play little part. In the study of the vascular system, Dr. Sheila Howarth observed that while a slow pulse and subnormal arterial pressures were the rule, it was usual to note elevated pressures in the great veins and the right auricle, and these pressures increased alarmingly when solutions were infused intravenously. The dangers of such procedures, in such conditions, are stressed. Many other types of clinical investigation are described in the various sections of the report.

D.L.T.

LA VECTOCARDIOGRAPHIE. By Pierre W. Duchosal and Robert Sulzer. New York, 1949, S. Karger, Ltd.

ETUDES PRATIQUES DE VECTOGRAPHIE. By E. Donzelot, J. B. Milovanovich, and H. Kaufman. Paris, 1950, L'Expansion Scientifique Française.

These two monographs in French are important additions to the literature on vectocardiography. Duchosal and Sulzer provide a thorough and clear treatment of vector principles and theory and thorough tests of the validity of their results. Although their vectograms are of superb quality, it is surely not reasonable these days to build one's equipment with single-ended, nondegenerative amplifiers. With better design it would be possible to have the patient resting in more comfort. These authors have studied the vectogram in great detail and have constructed four-dimensional wire models which are eloquent of the complex current generated about the heart.

After a clear description of the normal patterns of vectograms, the findings in left and right ventricular predominance and bundle branch block, ventricular infarction, and a few other conditions are described with admirable illustrations.

The second monograph proceeds more quickly to a description of pathological findings with far too little description of normal appearances and variation. However, a wealth of abnormal curves is presented. The method of presentation is a little different. The vectograms are recorded either on stationary film without time lines or on slowly moving film. Both books make

it clear that the possible variations in the vectographic patterns are formidable, and it is as well to consider what the clinical application of vectography is likely to be. It is possible that after much greater experience than is required for interpretation of conventional electrocardiograms one may learn to recognize the more important alterations in patterns. If this is so, it may be that the running film method of Donzelot and associates is the better method since the patterns are spread out and easier to follow through sequentially. Reference to these authors' Fig. 20 will show the complexity that can be attained even when just considering patterns. It seems that even if we consider only patterns, it is essential to have a time scale in order to recognize the temporal contribution of different parts of the vectogram to the electrocardiogram.

How much more can be learned by such an inspection of the vectogram than by unipolar electrocardiography is not clear; however, this much is certain, that at present satisfactory theoretical deductions about the state of activity in the various parts of the heart cannot be made with its help. To the present reviewer it seems that the vectogram may be of great value as an investigative tool for the intensive study of a few cardiac abnormalities, as the auricular arrhythmias, but it is not yet, if it will ever be, a routine method for the cardiologist.

A.S.V.B.

PHYSIOLOGY OF SHOCK. By C. J. Wiggers. New York, 1951, The Commonwealth Fund. Price $5.00.

The understanding of the mechanisms through which traumatic and hemorrhagic shock develops has proved one of the most difficult and untractable in physiology. A suitable analogy is perhaps the functioning of a radio; anyone after brief instruction can use a radio and make it perform within the limitations for which it is designed, but if a fault in its mechanism should develop, an entirely new and much more complex range of experience must be invoked to understand the fault and to service it. Our present understanding of the circulation is little better than the understanding of the householder who can use the radio; we are in desperate need of empirical remedies for its disorders, and our understanding of the fundamental principles of circulatory adjustments is pathetically sparse. Wiggers, whose experience in circulatory problems is vast, provides an admirable conspectus of the whole problem.

The definition of shock is difficult because the symptom-sign complex is variable. As Wiggers points out, the spectrum of classical signs and symptoms may be present without shock being present, and, on the other hand, none of these signs may be present when shock is impending. In experimental shock the patterns fall into two relatively well-defined groups, i.e., shock with a normal blood volume and shock with a reduced blood volume. These Wiggers terms normovolemic and oligemic shock. Much of the book is taken up with a critical discussion of standardized methods of producing shock. To the reviewer this is the most valuable part of the book, containing as it does such a detailed exposure of the defects of the methods used, because nowhere else in physiology is the dictum that the validity of results is limited by the validity of techniques so important.

The evidence now available is sufficient to reject the popular idea that the compensatory vasoconstriction in the early stages of shock leads to increased capillary permeability, plasma leakage into the tissues, and so a decrease in venous return. It is clear that the decreased venous return is due to a failure of the vasoconstriction and consequent peripheral pooling. Wiggers' evidence shows that in most cases of irreversible experimental shock there is also a myocardial failure as shown by the decreased responsiveness of the ventricle to increments of filling pressure. The most exciting work of recent years has suggested that the vascular changes are due to the production of vasotropic substances by ischemic tissues. As yet, however, this approach has not attained a sure footing, but it may well be that a closer study of the metabolic activity of ischemic tissues may provide the long sought for key to this important clinical problem. In conclusion, Dr. Wiggers' book will disappoint those readers who hoped for a simple answer, but its critical and comprehensive discussion will provide much food for thought.

A.S.V.B.

LOW-SODIUM DIET. A MANUAL FOR THE PATIENT. By Thurman B. Rice, M.D. Philadelphia, 1951, Lea & Febiger, 103 pages. Price $2.75.

The ease with which physicians today prescribe for the innocent cardiac patient the low-sodium diet or the so-called salt-free diet reminds one of the early days of dietary control of diabetes. The low-fat high-carbohydrate, or the high-fat low-carbohydrate, diet left the poor victim in a maze of difficulties, and particularly was this so for the harassed housewife who had to provide the diet either for herself or for another member of the family. It is well known to all how this situation led to diabetic classes, associated with large diabetic clinics.

The present volume contains the wisdom which was derived, apparently, the hard way by one who was condemned to the rigid regime of the low-sodium diet. The author pays just tribute to the marvelous job which dietitians have done in devising adequate palatable diets with this restriction. However, this is only part of the task. What may be effective in a department of dietetics of an institution is hard to translate to the kitchen of a household. The author, a physician himself and also one who has taught dietetics, pays further tribute to the key person who has made his life comfortable, namely, his wife, who, he says, is an excellent and original cook. Therefore, this book records first-hand experience of the difficulties surrounding a salt-free diet and how to surmount them. It should be on the kitchen shelf in every household where such a diet is prescribed and, perhaps of more importance, between the book ends on the desk of every physician who prescribes this diet for his patients.

J.C.M.

ARZNEITHERAPIE DER HERZKRANKHEITEN. By Hans-Jürgen Oettel, M.D. Stuttgart, 1951, Georg Thieme Verlag, 256 pages with 15 illustrations. Price DM 27.—.

The appearance of a volume devoted to the therapy of heart disease is always welcomed. This is particularly the case when it brings to the profession the outlook and experience of a school of thought from which we have been so long divorced.

In the present book, the author deals with the pharmacology of the digitalis glucosides as well as other drugs which affect the circulation in particular or in general. These principles are then applied to specific disorders and are integrated with the general disturbances which result therefrom.

For the serious student of the therapy of cardiac disease and its related functional disturbances, this volume contains much information and food for thought.

J.M.

DIE ORALE STROPHANTHIN-BEHANDLUNG. By Dr. Berthold Kern. Stuttgart, 1951, Ferdinand Enke Verlag, 382 pages. Price DM 21.—.

The present concentration upon digitalis and its glucosides in the treatment of heart disease has, unfortunately, practically excluded from our concept other drugs which have held a time-honored position, such as squill and strophanthus.

The author makes a special plea for the latter drug and supports this with many arguments and experimental evidence. Many of the former may be open to question, but, at the same time, they are well worthy of consideration. That strophanthus has a place in the medical treatment of cardiovascular disturbances cannot be lightly discarded.

This volume is deserving of the attention of those who wish to broaden their field of vision in the treatment of heart disease.

J.M.

CLINICAL ELECTROCARDIOGRAPHY. By Ashton Graybiel, Captain, Medical Corps, United States Navy. New York, 1951, Thomas Nelson & Sons, 198 pages with 140 illustrations. Price $5.00.

During the past few years, there have appeared a number of publications dealing with cardiology as a whole or restricted to some aspects of its study, and the electrocardiogram has taken a

prominent place among the latter. The present volume deals with electrocardiography in a simple straightforward fashion. It is introduced by three chapters in which terminology, the meaning of the electrocardiogram, and, finally, the technique and procedure are covered. The remainder of the book is devoted to the electrocardiogram in healthy persons and alterations due to physiological causes and certain drugs. Also dealt with are the changes in the electrocardiogram which are supposed to be attributable to specific types of cardiac lesions, and this portion is concise and brings up to date, as far as is possible in a book of this compass, the factual information as it is accepted today. The author has provided a book of ready and simple information for those who are not students of this phase of cardiology and who find it difficult to keep abreast of its interpretation.

J.M.

THE 1951 YEAR BOOK OF MEDICINE. Edited by Paul B. Beeson, M.D., J. Burns Amberson, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., and George B. Eusterman, M.D. Chicago, 1951, Year Book Publishers, Inc., 690 pages. Price $5.00.

The 1951 Year Book of Medicine continues to maintain the high standard set by its predecessors. The readers of this JOURNAL will be particularly interested in Part 4 which deals with the heart, the blood vessels, and the kidneys. In this section, there is a brief synopsis covering the more important publications during the past year on these subjects; therefore, it affords a predigested diet for the busy practitioner. For this reason, it fulfills a useful purpose. It is conspicuous, however, for its poverty of reference to publications outside of North America. If some of these could be included, the book would serve all the more to arouse curiosity and to inform readers as to the work which is being done by their colleagues in other countries.

J.M.

Announcement

Fourth Inter-American Cardiological Congress

The Fourth Inter-American Congress of Cardiology will be held in Buenos Aires from Aug. 31 to Sept. 7, 1952.

This Congress was organized by the Argentine Society of Cardiology. It is sponsored by the Inter-American Society of Cardiology and is under the auspices of the National Government.

Those who wish to participate as Titular members must ask for their registration before April 1, 1952 and must pay a fee of $250m/n. Relatives who wish to be registered as Associate members will pay a fee of $100.

Members who wish to present papers must send before April 1, 1952 and by way of the National Society of Cardiology to which they belong (or directly if there is no Society of Cardiology in their country) a summary that must not exceed 200 words and that is written, if possible, in Spanish or Portuguese and in English.

All correspondence should be addressed to the Office of the Administrative Secretary, Larrea 1132, Buenos Aires, Argentina.

Erratum

On page 816 of the December, 1951, issue in the article "Cardiovascular Disease in Marfan's Syndrome" by Robert J. Marvel and P. D. Genovese, the legends for Figs. 2 and 3 are reversed.

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Contents on Inside Cover

American Heart Journal

CONTENTS FOR MARCH, 1952

Original Communications

	Page
The Natural History of Uncomplicated Syphilitic Aortitis. Clayton Rich, Jr., M.D., and Bruce Webster, M.D., New York, N. Y.	321
The Cardiac Complications of Hemochromatosis. T. H. Bothwell, M.B., B.Ch., B. van Lingen, M.D., T. Alper, M.A., and M. L. du Preez, M.Sc., Johannesburg, South Africa	333
The Effect of Myxedema on the Cardiovascular System. Laurence B. Ellis, M.D., J. Gilmer Mebane, M.D., George Maresh, M.D., Herbert N. Hultgren, M.D., and Richard A. Bloomfield, M.D., Boston, Mass.	341
Studies of the Circulatory Dynamics at Rest in Mitral Valvular Regurgitation With and Without Stenosis. Richard Gorlin, M.D., Benjamin M. Lewis, M.D., Florence W. Haynes, Ph.D., and Lewis Dexter, M.D., Boston, Mass.	357
The Response of the Peripheral Venous Pressure to Exercise in Congestive Heart Failure. Roy E. Albert, M.D., and Ludwig W. Eichna, M.D., New York, N. Y.	395
Constrictive Pericarditis Caused by Solitary Metastatic Carcinosis of the Pericardium and Complicated by Radiation Fibrosis of the Mediastinum. S. R. Slater, M.D., I. G. Kroop, M.D., and S. Zuckerman, M.D., Brooklyn, N. Y.	401
Pericarditis in Patients With Leukemia. Howard R. Bierman, M.D., Evan K. Perkins, M.D., and Paul Ortega, M.D., San Francisco, Calif.	413
Left Atrial Enlargement. Harold G. Jacobson, M.D., Maxwell H. Poppel, M.D., Irwin B. Hanenson, M.D., and Stephen B. Dewing, M.D., New York, N. Y.	423
"Tent-Shaped" T Waves of Normal Amplitude in Potassium Intoxication. Harold D. Levine, M.D., Jehangir P. Vazifdar, M.D., Bernard Lown, M.D., and John P. Merrill, M.D., Boston, Mass.	437
The Use of Oral Quinidine and Procaine Amide as Premedications for Cardiac Catheterization. Willard J. Zinn, M.D., Richard S. Cosby, M.D., David C. Levinson, M.D., Harold Miller, M.D., Sim P. Dimitroff, M.D., Frank B. Cramer, and George C. Griffith, M.D., Los Angeles, Calif.	451
Electrocardiographic Changes Under Emetine Therapy. A. González de Cossio, M.D., Mexico City, Mexico	456

Clinical Reports

Coexistent Rheumatic Fever and Subacute Bacterial Endocarditis Treated With ACTH and Antibiotics. Colonel L. J. Numainville, Medical Corps, Army of the United States, and Lieutenant (jg) C. J. Scarpellino, United States Naval Reserve	468
Subacute Staphylococcus Aureus Endocarditis: Recovery Following Combined Antibiotic Therapy. William H. Harris, Jr., M.D., and George W. Fishburn, M.D., Richmond, Va.	474

Book Reviews

Book Reviews	479

Vol. 43, No. 3, March, 1952, American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, its Possessions, Pan-American Countries, $12.00; In Canada and other Foreign Countries, $13.00. Printed in the U. S. A.

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